CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074877

Trade Name : PENTOXIFYLLINE EXTENDED RELEASE TABLETS 400MG

Generic Name: Pentoxifylline Extended Release Tablets 400mg

Sponsor : ESI Lederle, Inc.

Approval Date: July 8, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074877

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074877

APPROVAL LETTER

ANDA 74-877

JUL 8 1997

ESI Lederle, Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River, NY 10965-1299

Dear Mr. Tantillo:

This is in reference to your abbreviated new drug application dated March 28, 1996, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Pentoxifylline Extended-release Tablets, 400 mg.

Reference is also made to your amendments dated November 26, and December 4, 1996; and July 7, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Pentoxifylline Extended-release Tablets, 400 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Trental® Tablets, 400 mg of Hoechst Marion Roussel Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application. The "interim" dissolution test(s) and tolerances are:

Dissolution - 1 hours =
6 hours =
10 hours =
20 hours =

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70 (c) (1) when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under 21 CFR 314.70 (b) (2) (ii).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

7/8/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

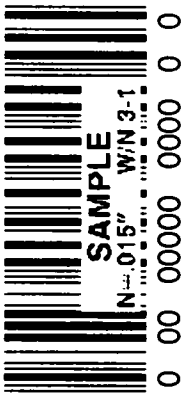
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074877

FINAL PRINTED LABELING

CODE INSERTED HERE

ESILEDERLE



UK 21907

NDC 59911-3290-3

ESI LEDERLE

Pentoxifylline Extended-release Tablets

400 mg

1000 Tablets

Caution: Federal law prohibits dispensing without prescription.

TAKE WITH MEALS.

Usual Dosage: See package circular for complete prescribing information.

Dispense in a well-closed, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

Store at controlled room temperature 15°-30°C (59°-86° F).

ESI Lederle Inc.
Philadelphia, PA 19101

UK 21907

UK 21907

CODE INSERTED HERE

ESILEDERLE

UK 21906

NDC 59911-3290-2

ESILEDERLE

Pentoxifylline Extended-release Tablets

400 mg

100 Tablets

Caution: Federal law prohibits dispensing without prescription.

TAKE WITH MEALS.

Usual Dosage: See package circular for complete prescribing information.

Dispense in a well-closed, light-resistant container with a child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86° F).

ESI Lederle Inc.
Philadelphia, PA 19101

UK 21906

UK 21906

NDC 59911-3290-2

ESI LEDERLE

Pentoxifylline
Extended-release
Tablets

400 mg

100 Tablets

Caution: Federal law prohibits dispensing without prescription.

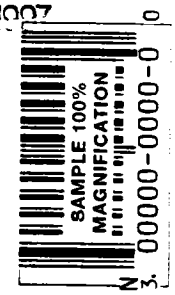
TAKE WITH MEALS.

Usual Dosage: See package circular for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a well-closed, light-resistant container with a child-resistant closure.

ESI Lederle Inc.
Philadelphia, PA 19101



Control No.:

Exp. Date:

U3290-02

NDC 59911-3290-3

ESI LEDERLE

Pentoxifylline
Extended-release
Tablets

400 mg

1000 Tablets

Caution: Federal law prohibits dispensing without prescription.

TAKE WITH MEALS.

Usual Dosage: See package circular for complete prescribing information.

Dispense in a well-closed, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

Store at controlled room temperature 15°-30°C (59°-86°F).

ESI Lederle Inc.
Philadelphia, PA 19101

U3290-03

Control No.:

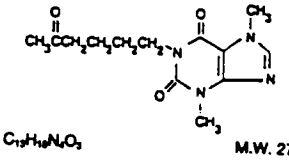
Exp. Date:

Pentoxifylline
Extended-release Tablets
400 mg

LEDERLE™

Description

Pentoxifylline Extended-release Tablets for oral administration contain 400 mg of the active drug and the following inactive ingredients: Hydroxyethylcellulose, Hydroxypropyl Methylcellulose USP, Magnesium Stearate NF, Polyethylene Glycol NF, Polysorbate 80 NF, Povidone USP, Talc USP, Titanium Dioxide USP. Pentoxifylline is a tri-substituted xanthine derivative designated chemically as 3,7-Dihydro-3, 7-dimethyl-1-(5-oxohexyl) -1*H*-purine-2, 6-dione that, unlike theophylline, is a hemorrheologic agent, i.e. an agent that affects blood viscosity. It has a molecular weight of 278.31. Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene. The chemical structure is:



$C_{13}H_{18}N_4O_3$ M.W. 278.31

Clinical Pharmacology

MODE OF ACTION

Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leukocyte properties of hemorrheologic importance have been modified in animal and *in vitro* human studies. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease.

PHARMACOKINETICS AND METABOLISM

After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing. Peak plasma levels of the parent compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxyhexyl]-3,7-dimethylxanthine) and Metabolite V (1-[3-carboxypropyl]-3, 7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than pentoxifylline.

Following oral administration of aqueous solutions containing 100 to 400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose-related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4 to 0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (Cytochrome P_{450}) following multiple oral doses.

Excretion is almost totally urinary; the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces. Food intake shortly before dosing delays absorption of an immediate-release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of pentoxifylline have not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years).

After administration of the 400 mg extended-release pentoxifylline tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2 to 4 hours and remain constant over an extended period of time. The controlled release of pentoxifylline from the tablet eliminates peaks and troughs in plasma levels for improved gastrointestinal tolerance.

Indications and Usage

Pentoxifylline extended-release tablets are indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Pentoxifylline can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

Contraindications

Pentoxifylline should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

Precautions

GENERAL

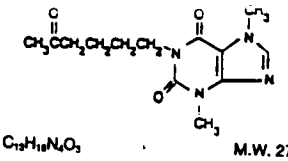
Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Pentoxifylline has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that pentoxifylline causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g. recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including hematocrit and/or hemoglobin.

DRUG INTERACTIONS

Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with pentoxifylline with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Concomitant administration of pentoxifylline and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals. Such patients should be closely monitored for signs of toxicity and have their theophylline dosage adjusted as necessary. Pentoxifylline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifylline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to 450 mg/kg (approximately 19 times the maximum recommended human daily dose [MRHD] in both species when based on body weight; 1.5 times the MRHD in the mouse and 3.3 times the MRHD in the rat when based on body-surface area). In mice, the drug was administered for 18 months, whereas in rats, the drug was administered for 18 months followed by an additional 6 months without drug exposure. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females of the 450 mg/kg group. The relevance of this finding to human use is uncertain. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test)



$C_{19}H_{18}N_4O_3$ M.W. 278.31

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PREGNANCY

Teratogenic Effects: Category C

Teratogenicity studies have been performed in rats and rabbits, using oral doses up to 576 and 264 mg/kg, respectively. On a weight basis, these doses are 24 and 11 times the maximum recommended human dose

(MRHD); on a body-surface-area basis, they are 4.2 and 3.5 times the MRHD. No evidence of fetal malformation was observed. Increased resorption was seen in rats of the 576 mg/kg group. There are no adequate and well-controlled studies in pregnant women. Pentoxifylline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

Adverse Reactions

Clinical trials were conducted using either extended-release pentoxifylline tablets for up to 60 weeks or immediate-release pentoxifylline capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg b.i.d. to t.i.d. and in the capsule studies, 200 to 400 mg t.i.d.

The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received extended-release pentoxifylline tablets, immediate-release pentoxifylline capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the extended-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE(%) OF SIDE EFFECTS

	Extended-release Tablets — Commercially Available		Immediate-release Capsules — Used Only for Controlled Clinical Trials	
	Pentoxifylline	**Placebo**	**Pentoxifylline**	**Placebo**
(Number of Patients at Risk)	(321)	(126)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	-	1.1	2.2
Arrhythmia/Palpitation	-	-	1.7	0.7
Flushing	-	-	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	-	-	4.0	1.4
Belching/Flatus/Bloating	0.6	-	8.0	3.6
Diarrhea	-	-	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	-	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	-	-	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	-	-	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	-	-	2.3	2.2
Tremor	0.3	0.8	-	-
Blurred Vision	-	-	2.3	1.4

Pentoxifylline has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:

Cardiovascular

dyspnea, edema, hypotension

Digestive

anorexia, cholecystitis, constipation, dry mouth/thirst

Nervous

anxiety, confusion, depression, seizures

Respiratory

epistaxis, flu-like symptoms, laryngitis, nasal congestion

Skin and Appendages

brittle fingernails, pruritus, rash, urticaria, angioedema

Special Senses

blurred vision, conjunctivitis, earache, scotoma

Miscellaneous

bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: "Cardiovascular—angina, arrhythmia, tachycardia, anaphylactoid reactions." Digestive—hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

Overdosage

Overdosage with pentoxifylline has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.

In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to adsorb pentoxifylline in patients who have overdosed.

Dosage and Administration

The usual dosage of pentoxifylline in extended-release tablet form is one tablet (400 mg) three times a day with meals.

While the effect of pentoxifylline may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.

Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of pentoxifylline should be discontinued.

How Supplied

Pentoxifylline Extended-release Tablets, 400 mg, are oblong shaped, unscored, white, film-coated tablets engraved with "511" on one side and "P77" on the other side and are supplied as follows:

NDC 59911-3290-2 - Bottle of 100 with CRC

NDC 59911-3290-3 - Bottle of 1000

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in well-closed, light-resistant containers.

Caution: Federal law prohibits dispensing without prescription.

ESI Lederle Inc.
Philadelphia, PA 19101
CI 4641 Issued November 11 1996 Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074877

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-877

3. NAME AND ADDRESS OF APPLICANT
ESI Lederle, Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River, NY 10965-1299

4. Patent Exclusivity
The drug is not entitled to a period of marketing exclusivity. It is covered by two U.S. patents expiring on February 2, 1997 and April 3, 1997, respectively.

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Pentoxifylline

9. AMENDMENTS AND OTHER DATES:

Orig Sub.	3/28/96
Ack. Ltr	4/24/96
NA Letter	10/23/96
Amendment	11/26/96

10. PHARMACOLOGICAL CATEGORY
Vasodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

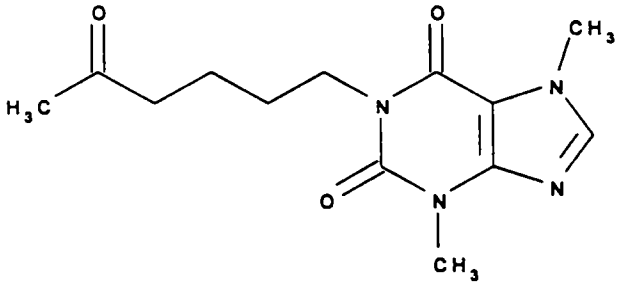
13. DOSAGE FORM
Ext. release tablet

14. POTENCY
400 mg

15. CHEMICAL NAME AND STRUCTURE

Pentoxifylline

$C_{13}H_{18}N_4O_3$; M.W. = 278.31



3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione.
CAS [6493-05-6]

17. COMMENTS
See text of review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER: DATE COMPLETED:
Andrew J. Langowski 3/10/97;6/17/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074877

BIOEQUIVALENCE REVIEW(S)

OCT 2 3 1996

Pentoxifylline
400 mg Extended Release Tablets
ANDA #74-877
Reviewer: Z.Z. Wahba
File #74877sd.396

ESI Lederle
Pearl River, NY
Submission Date:
March 28, 1996

REVIEW OF THREE IN VIVO BIOEQUIVALENCE STUDIES, AND IN VITRO DISSOLUTION TESTING DATA

I. OBJECTIVE:

To review:

1. ESI Lederle's three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple dose) comparing its test product Pentoxifylline 400 mg Extended Release Tablets to the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets.

2. Dissolution profiles comparing ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets to the reference listed drug Hoechst-Roussel's Trental® 400 mg Extended Release Tablets.

Studies Included in Submission:

1. A two-way crossover, single-dose bioequivalence study of Pentoxifylline 400 mg Extended Release Tablets under fasting conditions (clinical study project #013-20-10895).

2. A three-way crossover, single-dose, post-prandial bioequivalence study of Pentoxifylline 400 mg Extended Release Tablets (clinical study project #013-21-10896).

3. A two-way crossover, steady-state, multiple-dose bioequivalence study of Pentoxifylline 400 mg Extended Release Tablets (clinical study project #013-22-10897).

II. BACKGROUND:

Pentoxifylline is a hemorheologic agent that improves the flow properties of blood by decreasing its viscosity and improving erythrocyte flexibility. These actions increase blood flow and enhance tissue oxygenation in patients with chronic peripheral arterial disease. It is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still unclear.

After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass metabolism by both oxidation and reduction pathways. Peak plasma levels of the parent

compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxyhexyl]-3,7-dimethylxanthine) and metabolite V (1-[3-carboxypropyl]-3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than pentoxifylline. Following oral administration of aqueous solution containing 100 to 400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4 to 0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. Excretion is almost totally urinary; the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of the parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces.

Food intake shortly before dosing delays absorption of an immediate release dose form but does not affect total absorption. After administration of the 400 mg controlled release pentoxifylline tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2 to 4 hours and remain constant over an extended period of time.

Pentoxifylline is available as Trental® (Hoechst-Roussel) 400 mg Extended Release Tablets. The usual dosage is one tablet three times a day with meals.

III. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING CONDITIONS

(clinical study project #013-20-10895)

A. **Sponsor:**
ESI-Lederle
401 N. Middletown Road
Pearl River, NY 10965

Study site
Clinical Facilities

Study Dates:
Phase I: September 08-11, 1995
Phase II: September 15-17, 1995

B. **Study design:**

Randomized, single dose, two-way crossover study, under fasting conditions.

C. **Subjects:**

Forty-two (42) healthy male subjects were enrolled but 41 subjects completed the clinical study. Subject #28 voluntarily withdrew after completing period I and before period II.

The subjects were in the range of 20 to 39 years of age, and their body weights were within ± 15% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:

Only medically healthy subjects as determined by normal history, physical examination, laboratory profiles and ECG were enrolled in the study.

Subject Exclusion Criteria:

Subjects were excluded from the study based on the following criteria:

1. History of cardiovascular, pulmonary, gastrointestinal, endocrine, neurologic, hematological, hepatic or renal disease.
2. History of angioedema or asthma.
3. Hypersensitivity to pentoxifylline or other related drugs.
4. A history of chronic alcohol or drug addiction.
5. Use of tobacco in any form.
6. Blood donation within the past 60 days of the study.
7. Receiving any investigational drug within 30 days prior to period I dosing.

Subject Restrictions:

1. No subject took any medications, including OTC products for at least 14 days prior to the beginning of the study until completion of the study.
2. No alcohol, xanthine and caffeine containing foods and beverages were allowed, beginning 24 hours prior to dosing until completion of the study.

D. **Treatment Plan:**

Test Product: 1 X 400 mg ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets, Lot #93250-0100, Batch size tablets, assay potency 97.3%, content uniformity 100.2% (%CV=2.0), expiration date 06/20/1996.

Reference Product: 1 X 400 mg Hoechst-Roussel's Trental® 400 mg Extended Release Tablets, Lot #0781255, assay potency 99.8%, content uniformity 101.3% (%CV=1.0), expiration date: April 1997.

Washout period: one week between doses.

E. **Drug, Food and Fluid Intake:**

Subjects fasted overnight (10 hours) before dosing and for 5 hours thereafter. Water ad libitum was allowed until 1 hour before dosing and 2 hours after dosing. The subjects received their medication with 180 mL of water. Standard meals were provided at appropriate times thereafter (lunch at 5 hours, supper at 10 hours post-dose).

F. **Blood sampling:**

Blood samples (1X10 mL each) were collected in EDTA Vacutainers at 0.0 (pr-dosing), 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, 12, 14, 16, 20 and 24 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -70 °C until analysis.

G. **ASSAY METHODOLOGY:**

H. **Safety Monitoring:**
Vital signs (blood pressure and pulse) were measured pre-dose and at 2, 4 and 24 hours post-dose. Diagnostic blood and urine specimens were obtained from all subjects prior to discharge from the study at the end of period-2. No clinically significant changes were observed.

I. **Adverse Events:**
The adverse reactions have been reported (Vol. C1.2, p 177 & 178). Sixteen subjects reported 9 adverse events. The most frequently reported events were headache (4 subjects) and decreased diastolic blood pressure (5 subjects). All the events were mild. The conclusion of the medical report were that there were no significant or unexpected drug related adverse events and both products appear to be equally well tolerated.

J. **In Vivo Data Analysis:**
Forty-two (42) healthy male subjects were enrolled but 41 subjects completed the clinical study. Subject #28 voluntarily withdrew after completing period I and before period II.

All samples (from the 41 subjects who completed the study) were assayed. However, assay results from the following subjects were not reported for the respective analytes because no analytically valid data were obtained.

Pentoxifylline: subjects #11, #26, #30, #31, #35, #38 and #39

Metabolite I: subjects #14, #17 and #30
Metabolite V: subject #30

Note: see the Deficiency Section, comment #1.

There were 34 sets of data used in the analysis of pentoxifylline, 38 sets of data used for the analysis of metabolite I and 40 sets for metabolites V.

Table 1
Mean Plasma Concentrations of Pentoxifylline in 34 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN1/2
0	0.15	0.88	0.22	1.31	0.67
0.33	33.59	31.90	34.28	28.29	0.98
0.67	**60.25**	38.72	**59.54**	27.73	**1.01**
1	57.29	34.20	53.38	24.06	1.07
1.33	54.28	35.07	51.40	23.11	1.06
1.67	53.82	28.46	46.40	20.30	1.16
2	53.30	33.96	48.67	28.29	1.10
2.33	49.30	28.60	49.82	29.72	0.99
2.67	45.79	28.82	45.18	29.77	1.01
3	43.58	23.74	42.74	27.57	1.02
3.5	39.75	20.08	37.76	28.58	1.05
4	36.26	22.28	35.20	22.78	1.03
5	33.58	25.06	34.20	29.21	0.98
6	43.70	34.10	45.52	31.71	0.96
8	35.17	25.73	33.95	25.42	1.04
10	27.20	17.39	30.41	20.63	0.89
12	28.61	16.53	34.04	24.44	0.84
14	26.52	21.54	30.92	23.53	0.86
16	22.10	21.19	21.19	18.77	1.04
20	8.37	10.62	6.65	8.79	1.26
24	1.80	4.18	2.69	6.41	0.67

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 2
Arithmetic and Geometric Mean
Pentoxifylline Pharmacokinetic Parameters
in 34 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet
under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN1/2
AUCI	785.34	424.18	817.22	427.31	0.96
AUCT	612.88	380.17	621.92	376.66	0.99
CMAX	76.82	41.59	74.86	32.86	1.03
THALF	3.56	1.82	5.22	3.56	0.68
TMAX	2.43	3.20	2.26	2.86	1.08
KE	0.24	0.10	0.18	0.10	1.30
*LAUCI	689.40		733.55		0.94
*LAUCT	519.33		535.69		0.97
*LCMAX	67.09		68.42		0.98

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 3
LSMEANS AND 90% CONFIDENCE INTERVALS
in 34 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet

	LSMEAN1	LSMEAN2	T/R	LOWCI1/2	UPPCI1/2
AUCI	739.38	767.83	0.96	88.31	104.28
AUCT	608.88	619.62	0.98	92.22	104.31
CMAX	76.39	74.87	1.02	93.86	110.21
***LAUCI**	**656.89**	**677.69**	**0.97**	**90.29**	**104.06**
***LAUCT**	**514.46**	**534.45**	**0.96**	**87.83**	**105.49**
***LCMAX**	**66.60**	**68.37**	**0.97**	**89.23**	**106.32**

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
T/R= Test/Ref. ratios (under fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the LSMEAN (antilog of the means of the logs).

1. The mean plasma pentoxifylline levels reached a maximum level of concentration around 0.67 hour (Table #1 and the attached Figure #1).

2. The 90% confidence intervals based on the LSMEAN for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range

of 80-125% (Table #3). The T/R mean ratios of the LSMEAN for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were 0.96, 0.97 and 0.97 , respectively (Table #3).

There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

3. The average mean for $T_{1/2}$, T_{max} and K_{el} values were 32% lower, 8% higher and 30% higher, respectively, for the test product than for the reference product (Table #2).

Table 4
Mean Plasma Concentrations of Metabolite I in 38 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN1/2
0	2.05	7.63	1.86	6.66	1.10
0.33	35.08	33.52	43.90	40.54	0.80
0.67	120.34	69.78	129.68	74.65	0.93
1	177.51	95.40	180.30	88.81	0.98
1.33	206.93	110.27	206.88	95.21	1.00
1.67	222.58	109.50	206.08	83.36	1.08
2	234.54	114.01	230.51	98.87	1.02
2.33	**239.77**	120.24	**235.41**	109.52	**1.02**
2.67	234.91	118.02	232.61	118.02	1.01
3	230.30	113.05	222.62	114.22	1.03
3.5	217.46	104.88	217.65	119.36	1.00
4	206.94	98.74	210.51	116.36	0.98
5	182.81	89.37	195.22	104.56	0.94
6	178.09	90.45	180.38	101.50	0.99
8	133.63	76.92	136.77	77.49	0.98
10	117.67	70.75	135.23	81.62	0.87
12	111.44	68.65	122.74	72.49	0.91
14	103.68	62.21	116.07	71.02	0.89
16	87.36	58.01	84.43	52.04	1.03
20	42.66	36.77	36.59	34.73	1.17
24	16.07	23.27	14.75	21.54	1.09

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 5
Arithmetic and Geometric Mean
Metabolite I Pharmacokinetic Parameters
in 38 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet
under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN1/2
AUCI	2906.07	1489.32	3000.68	1445.37	0.97
AUCT	2665.45	1384.78	2740.18	1374.94	0.97
CMAX	258.67	123.89	260.15	121.19	0.99
THALF	3.48	1.40	3.70	1.89	0.94
TMAX	2.64	1.12	3.50	3.00	0.75
KE	0.24	0.13	0.24	0.11	1.03
*LAUCI	2549.65		2654.51		0.96
*LAUCT	2319.47		2398.90		0.97
*LCMAX	229.29		234.09		0.98

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 6
LSMEANS AND 90% CONFIDENCE INTERVALS (Metabolite I)
in 38 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet

	LSMEAN1	LSMEAN2	T/R	LOWCI1/2	UPPCI1/2
AUCI	2866.51	2984.79	0.96	91.23	100.84
AUCT	2669.91	2739.01	0.97	92.48	102.48
CMAX	258.90	259.24	1.00	94.79	104.94
***LAUCI**	**2509.72**	**2654.93**	**0.95**	**88.74**	**100.70**
***LAUCT**	**2320.39**	**2397.76**	**0.97**	**90.80**	**103.13**
***LCMAX**	**229.20**	**233.27**	**0.98**	**93.36**	**103.40**

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
T/R= Test/Ref. ratios (under fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the LSMEAN (antilog of the means of the logs).

1. The mean plasma metabolite I levels reached a maximum level of concentration around 2.33 hours (Table #4 and the attached Figure #2).

2. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #6).

The T/R mean ratios of the LSMEAN for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were 0.97, 0.95 and 0.98 , respectively (Table #6).

There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

3. The average mean values of the parameters $T_{1/2}$ and K_{el} for the test product were similar to that of the reference product. The average mean value of the T_{max} for the test product was lower by 25% as compared to the reference product (Table #5).

Table 7
Mean Plasma Concentrations of Metabolite V in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN1/2
0	0.00	0.00	0.00	0.00	.
0.33	145.24	93.64	183.76	134.81	0.79
0.67	406.45	132.53	466.15	171.95	0.87
1	525.93	122.01	562.68	156.42	0.93
1.33	546.97	131.98	550.13	138.30	0.99
1.67	562.83	116.18	555.90	143.10	1.01
2	**563.08**	130.59	**578.28**	127.37	**0.97**
2.33	562.90	141.13	563.50	143.55	1.00
2.67	525.00	126.51	547.98	147.43	0.96
3	505.77	132.81	518.53	163.64	0.98
3.5	473.88	127.61	474.40	156.95	1.00
4	442.38	140.88	459.08	137.26	0.96
5	396.03	135.66	417.20	149.97	0.95
6	368.85	111.66	392.18	118.49	0.94
8	290.97	110.75	301.65	108.33	0.96
10	256.38	108.67	309.64	120.28	0.83
12	228.85	93.14	263.00	106.13	0.87
14	229.54	107.35	265.74	101.71	0.86
16	201.01	90.36	205.36	80.10	0.98
20	94.05	61.29	92.07	59.20	1.02
24	32.74	49.81	28.36	45.00	1.15

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 8
Arithmetic and Geometric Mean
Metabolite V Pharmacokinetic Parameters
in 40 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet
under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN1/2
AUCI	6476.53	1538.68	6967.52	1409.41	0.93
AUCT	5989.08	1466.59	6361.95	1355.75	0.94
CMAX	635.40	131.02	653.05	131.93	0.97
THALF	3.18	1.59	3.71	2.33	0.86
TMAX	1.90	0.87	1.82	0.89	1.05
KE	0.26	0.12	0.25	0.12	1.07
*LAUCI	6265.67		6813.18		0.92
*LAUCT	5790.75		6213.68		0.93
*LCMAX	622.03		640.00		0.97

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 9
LSMEANS AND 90% CONFIDENCE INTERVALS
For Metabolite V in 40 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet

	LSMEAN1	LSMEAN2	T/R	LOWCI1/2	UPPCI1/2
AUCI	6299.88	6883.05	0.92	86.21	96.85
AUCT	5989.08	6361.95	0.94	90.06	98.22
CMAX	635.40	653.05	0.97	94.38	100.21
***LAUCI**	**6070.50**	**6713.43**	**0.90**	**84.58**	**96.67**
***LAUCT**	**5790.75**	**6213.68**	**0.93**	**88.20**	**98.47**
***LCMAX**	**622.03**	**640.00**	**0.97**	**94.31**	**100.16**

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
T/R= Test/Ref. ratios (under fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the LSMEAN (antilog of the means of the logs).

1. The mean plasma metabolite V levels reached a maximum level of concentration around 2.0 hours (Table #7 and the attached Figure #3).

2. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #9).

The T/R mean ratios of the LSMEAN for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were 0.93, 0.90 and 0.97 , respectively (Table #9).

There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters C_{max}.

For the AUC_{0-t} and $AUC_{0-\infty}$, there were no significant sequence and period effects of the test and reference drug treatments. However, there was a significant treatment effect (p less than 0.05) for the log-transformed pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$.

3. The average mean values of the parameters T_{max} and K_{el} for the test product were similar to that of the reference product. The average mean value of the $T_{1/2}$ for the test product was lower by 14% as compared to the reference product (Table #8).

IV. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER NON-FASTING CONDITIONS (clinical study project #013-21-10896)

A. Sponsor:
ESI-Lederle
401 N. Middletown Road
Pearl River, NY 10965

Study site
Clinical Facilities

Study Dates:
Phase I: October 27-29, 1995
Phase II: November 03-05, 1995
Phase III: November 10-12, 1995

B. Study design:
Randomized, three-way single dose crossover study, under non-fasting conditions.

C. Subjects:
Twenty one (21) healthy male subjects were enrolled but only 18 completed all periods of the clinical study. Subject #6 did not return for period 2. Subject #7 was late for period 2, and was withdrawn for non-compliance and subject #21 tested positive for cocaine at period 2 check-in.

D. **Treatment Plan:**

Treatment A: 1 X 400 mg ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets, Lot #93250-0100, Batch size tablets, assay potency 97.3%, content uniformity 100.2% (%CV=2.0), expiration date 06/20/1996, under non-fasting conditions.

Treatment B: 1 X 400 mg Hoechst-Roussel's Trental® 400 mg Extended Release Tablets, Lot #0781255, assay potency 99.8%, content uniformity 101.3% (%CV=1.0), expiration date: April 1997, under non-fasting condition.

Treatment C: 1 X 400 mg ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets, Lot #93250-0100, Batch size tablets, assay potency 97.3%, content uniformity 100.2% (%CV=2.0), expiration date 06/20/1996, under fasting conditions.

Washout period: one week between doses.

E. **Drug, Food and Fluid Intake:**

Subjects who received treatments A and B, fasted overnight for 10 hours before they were fed a standard high fat breakfast, which was consumed in its entirety 15 minutes before drug administration. Each dose was followed by 180 mL of room temperature tap water according to randomized dosing schedule. Water was allowed ad lib except for 1 hour before dosing and until 2 hours after dosing. Subjects who received treatment C, fasted overnight for 10 hours before dosing and for 4 hours after each drug administration. Standard meals were provided at appropriate times thereafter (lunch at 5 hours, supper at 10 hours post-dose).

F. **Blood sampling:**

Blood samples (1X10 mL each) were collected in EDTA Vacutainers at 0.0 (pr-dosing), 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, 12, 14, 16, 20 and 24 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -70 °C until analysis.

G. **Adverse Events:**

The adverse reactions have been reported (Vol. C1.7, p 1973). Seven subjects reported a total of 16 adverse events. Headache was the most frequently reported event (5 subjects, 9 events). All the events were mild. The conclusion of the medical report that there were no significant or unexpected drug related adverse events and both products appear to be equally well tolerated.

H. **Assay Methodology:**

Methods and Validation:

Similar to the clinical study protocol #013-20-10895, under fasting conditions.

I. **Data Analysis:**

Twenty one (21) healthy male subjects were enrolled but only 18 completed all periods of the clinical study. Subject #6 did not return for period 2. Subject #7 was late for period 2, and was withdrawn for non-compliance and subject #21 tested positive for cocaine at period 2 check-in. The pharmacokinetic parameters of the plasma pentoxifylline, metabolite I and metabolite V concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf} and C_{max} are summarized in Tables #10 & 11.

Table 10
Mean Plasma Concentrations of Pentoxifylline
18 Subjects Following a Single-Dose of
Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	11.38	17.91	9.71	10.43	36.31	38.68
0.67	25.91	29.19	23.17	15.86	58.13	42.58
1	35.79	24.85	32.87	19.41	51.44	28.43
1.5	52.31	27.49	47.82	33.69	49.37	34.57
2	54.97	31.30	53.41	35.03	49.56	29.90
2.5	61.67	33.12	56.20	35.86	42.67	28.32
3	64.57	36.42	59.58	33.78	41.54	27.56
3.5	63.34	37.45	57.69	30.42	40.86	26.88
4	68.74	47.87	58.42	26.81	32.63	23.21
4.5	75.46	56.94	67.41	37.83	28.41	18.55
5	74.72	49.88	75.49	50.29	26.28	15.34
6	**84.85**	61.92	**85.18**	69.40	35.34	20.96
8	42.79	32.13	47.44	43.25	35.64	26.18
10	56.36	63.70	26.80	15.32	27.93	16.16
12	33.39	34.17	26.68	26.03	23.13	17.89
14	14.10	12.02	14.10	9.78	20.02	17.99
16	8.87	9.42	6.45	6.58	12.55	11.06
20	0.71	2.06	0.73	2.19	6.07	8.58
24	0.00	0.00	0.00	0.00	3.43	5.16

(CONTINUED)

TIME HR	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
0.33	1.17	0.31	0.27
0.67	1.12	0.45	0.40
1	1.09	0.70	0.64
1.5	1.09	1.06	0.97
2	1.03	1.11	1.08
2.5	1.10	1.45	1.32

3	1.08	1.55	1.43
3.5	1.10	1.55	1.41
4	1.18	2.11	1.79
4.5	1.12	2.66	2.37
5	0.99	2.84	2.87
6	**1.00**	2.40	2.41
8	0.90	1.20	1.33
10	2.10	2.02	0.96
12	1.25	1.44	1.15
14	1.00	0.70	0.70
16	1.37	0.71	0.51
20	0.97	0.12	0.12
24	.	0.00	0.00

MEAN1=Test-Fed MEAN2=Reference-Fed MEAN3=Test-Fast
RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 11
LSMEANS Pharmacokinetic Parameters Pentoxifylline in 18 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Non-Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	918.94	797.76	713.48	1.15	1.29	1.12
AUCT	761.98	668.65	565.49	1.14	1.35	1.18
CMAX	136.62	125.75	80.23	1.09	1.70	1.57
***LAUCI**	**842.16**	**754.66**	657.39	**1.12**	1.28	1.15
***LAUCT**	**649.80**	**598.57**	438.98	**1.09**	1.48	1.36
***LCMAX**	**119.54**	**111.01**	64.83	**1.08**	1.84	1.71

LSM1=LSMEAN Test-Fed LSM2=LSMEAN Ref.-Fed LSM3=LSMEAN Test-Fast
RLSM12=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the LSMEAN (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma levels for pentoxifylline reached the maximum around 6.0 hours (Table #10 and Figure #4).

2. Under non-fasting conditions, the T/R mean ratios of the LSMEAN for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence (Table #11).

Table 12
Mean Plasma Concentrations of Metabolite I
18 Subjects Following a Single-Dose of
Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	11.28	26.84	9.31	12.95	42.68	47.07
0.67	44.20	48.64	48.83	46.35	146.17	117.96
1	81.06	73.66	78.85	55.38	201.74	143.12
1.5	136.81	83.43	127.14	76.30	231.10	132.61
2	177.29	102.04	166.38	100.35	243.60	131.18
2.5	206.18	108.16	194.76	114.20	241.65	126.80
3	230.60	122.11	224.50	129.01	238.24	127.87
3.5	276.44	144.05	233.82	120.63	235.24	126.65
4	295.36	161.46	256.71	122.09	215.47	112.99
4.5	326.22	204.90	280.31	135.06	194.43	111.71
5	344.28	207.19	335.56	180.37	183.35	103.49
6	368.81	229.29	335.09	181.72	160.92	80.23
8	221.53	156.52	240.68	175.68	135.42	76.89
10	195.44	157.46	154.57	112.27	121.98	67.40
12	153.36	148.67	124.52	93.36	97.41	61.10
14	84.33	69.41	73.97	45.69	82.55	63.00
16	52.16	49.89	46.57	29.52	71.08	69.14
20	14.88	18.69	14.44	13.52	39.38	40.32
24	2.34	5.58	1.57	4.61	21.66	25.32

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.33	1.21	0.26	0.22
0.67	0.91	0.30	0.33
1	1.03	0.40	0.39
1.5	1.08	0.59	0.55
2	1.07	0.73	0.68
2.5	1.06	0.85	0.81
3	1.03	0.97	0.94
3.5	1.18	1.18	0.99
4	1.15	1.37	1.19
4.5	1.16	1.68	1.44
5	1.03	1.88	1.83
6	1.10	2.29	2.08
8	0.92	1.64	1.78
10	1.26	1.60	1.27

12	1.23	1.57	1.28
14	1.14	1.02	0.90
16	1.12	0.73	0.66
20	1.03	0.38	0.37
24	1.50	0.11	0.07

MEAN1=Test-Fed MEAN2=Reference-Fed MEAN3=Test-Fast
RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 13
LSMEAN Pharmacokinetic Parameters Metabolite I in 18 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Non-Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	3355.16	3130.68	2944.85	1.07	1.14	1.06
AUCT	3299.15	2993.81	2704.18	1.10	1.22	1.11
CMAX	484.59	422.10	274.15	1.15	1.77	1.54
***LAUCI**	**2947.02**	**2844.10**	2591.77	**1.04**	1.14	**1.10**
***LAUCT**	**2894.92**	**2678.13**	2294.34	**1.08**	1.26	**1.17**
***LCMAX**	**429.55**	**379.89**	230.46	**1.13**	1.86	**1.65**

LSM1=LSMEAN Test-Fed LSM2=LSMEAN Ref.-Fed LSM3=LSMEAN Test-Fast
RLSM12=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the LSMEAN (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma levels for metabolite I reached the maximum around 5.0-6.0 hours (Table #12 and Figure #5).

2. Under non-fasting conditions, the T/R mean ratios of the LSMEAN for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence (Table #13).

Table 14
Mean Plasma Concentrations of Metabolite V
18 Subjects Following a Single-Dose of
Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	30.96	54.83	20.85	25.89	162.13	136.93
0.67	118.56	89.09	113.92	67.41	419.11	182.66
1	193.04	118.61	205.88	107.17	523.50	172.75
1.5	316.61	157.14	305.00	165.76	554.61	124.73
2	359.61	159.62	368.33	180.23	537.33	150.01
2.5	422.72	203.87	421.83	224.45	509.39	148.74
3	484.44	297.96	477.78	249.88	480.94	109.58
3.5	559.94	333.62	488.72	233.34	476.78	127.98
4	593.00	304.80	555.67	227.14	428.39	119.62
4.5	**640.06**	323.05	618.89	269.89	390.17	103.28
5	639.89	266.26	**702.39**	256.23	365.22	99.59
6	588.89	175.44	616.22	166.45	331.50	108.45
8	319.72	118.71	407.61	216.56	277.28	89.57
10	372.17	287.03	283.83	125.04	249.06	91.71
12	275.27	219.41	254.06	224.80	198.36	70.96
14	146.83	83.66	165.58	136.89	181.40	83.05
16	98.35	65.33	117.10	107.55	185.93	184.01
20	21.95	31.44	31.35	31.37	99.42	81.35
24	3.79	11.25	3.41	9.94	61.38	66.69

(CONTINUED)

TIME HR	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
0.33	1.48	0.19	0.13
0.67	1.04	0.28	0.27
1	0.94	0.37	0.39
1.5	1.04	0.57	0.55
2	0.98	0.67	0.69
2.5	1.00	0.83	0.83
3	1.01	1.01	0.99
3.5	1.15	1.17	1.03
4	1.07	1.38	1.30
4.5	**1.03**	1.64	1.59
5	**0.91**	1.75	1.92
6	0.96	1.78	1.86
8	0.78	1.15	1.47
10	1.31	1.49	1.14
12	1.08	1.39	1.28

14	0.89	0.81	0.91
16	0.84	0.53	0.63
20	0.70	0.22	0.32
24	1.11	0.06	0.06

MEAN1=Test-Fed MEAN2=Reference-Fed MEAN3=Test-Fast
RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 15
LSMEAN Pharmacokinetic Parameters Metabolite V in 18 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Non-Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	5860.80	6009.56	6311.77	0.98	0.93	0.95
AUCT	5642.94	5768.47	5673.60	0.98	0.99	1.02
CMAX	880.43	832.13	610.79	1.06	1.44	1.36
***LAUCI**	**5772.08**	**5889.88**	6056.64	**0.98**	0.95	**0.97**
***LAUCT**	**5546.26**	**5639.46**	5492.65	**0.98**	1.01	**1.03**
***LCMAX**	**837.33**	**796.25**	597.54	**1.05**	1.40	**1.33**

LSM1=LSMEAN Test-Fed LSM2=LSMEAN Ref.-Fed LSM3=LSMEAN Test-Fast
RLSM12=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the LSMEAN (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma levels for metabolite V reached the maximum around 4.5-5.0 hours (Table #14 and Figure #6).

2. Under non-fasting conditions, the T/R mean ratios of the LSMEAN for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence (Table #15).

V. MULTIPLE DOSE BIOEQUIVALENCE STUDY
(clinical study project #013-22-10897)

The objective of the study to assess the bioequivalence of ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets at steady-state levels compared to the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets following a single 400 mg oral dose of pentoxifylline every 8 hours for 13 doses each study phase.

A. Sponsor:
ESI-Lederle

401 N. Middletown Road
Pearl River, NY 10965

Study site
Clinical Facilities

Study Dates:
Phase I: October 31-November 05, 1995
Phase II: November 12-17, 1995

B. Study design:
Randomized, multiple-dose (every 8 hours for 13 doses in each study phase), steady-state, two-way crossover design, under fasting conditions.

C. Subjects:
Twenty-six (26) healthy male subjects entered the clinical study but only 24 subjects completed the entire clinical portion of the study. Subject #10 failed to return to the facility for period 2 and subject #13 withdrew during period 2, Day 2 before the morning dose because of cold symptoms.

D. Subject Selection, Exclusion and Restriction Criteria:
Similar to study protocol # 013-20-10895

E. Treatment Plan:
Test Product: 1 X 400 mg ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets, Lot #93250-0100, Batch size tablets, assay potency 97.3%, content uniformity 100.2% (%CV=2.0), expiration date 06/20/1996.

Reference Product: 1 X 400 mg Hoechst-Roussel's Trental® 400 mg Extended Release Tablets, Lot #0781255, assay potency 99.8%, content uniformity 101.3% (%CV=1.0), expiration date: April 1997.

Washout period: one week between doses.

F. Drug, Food and Fluid Intake:
For Days 1-4: The subjects fasted overnight (for 10 hours) the evening prior to each study day until 7:00 am (dosing time). A 400 mg tablet of the test or reference product was given every 8 hours and was administered with 180 mL of water at 0700, 1500 and 2300 hour for 4 days.

For Day 5: The subjects fasted overnight (for 10 hours) prior to dosing and until 5 hours after dosing on Day-5. A 400 mg tablet of the test or reference product was administered with 180 mL water at 0700 hour (dosing time).

Water was allowed ad-lib except for 2 hours pre-dose and 2 hours post-dose on Day 5, and within one hour of dosing on Day 1 to Day 4. Identical meal plans were served to all study subjects for both study periods.

Note: Each formulation (test and reference) was administered each day three times (at 0700, 1500 and 2300 hour for 4 days) and only one dose on Day 5 (at 0700 hour).

G. **Blood samples:**

Blood samples (1X10 mL each) were collected from each subject according to the following schedule:

Day 1: 0 hour (pre-drug) at 7:00 am
Day 2: 24 hours (pre-drug) at 7:00 am
Day 3: 48 hours (pre-drug) at 7:00 am
Day 4: 72 hours (pre-drug) at 7:00 am
Day 5: 96 hours (pre-drug, at 7:00 am), 96.25, 96.5, 97.0, 97.5, 98, 98.5, 99.0, 99.5, 100, 101, 102, 103, and 104 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -70 °C until analysis.

H. **Adverse Events:**

The adverse reactions have been reported (Vol. C1.11, p 3383 & 3384). Twelve subjects reported 22 adverse events. All the events were mild. No treatment was administered for adverse events experienced during this study except subject #22 had taken Tylenol to treat cold symptoms. The conclusion of the medical report that there were no significant or unexpected drug related adverse events and both products appear to be equally well tolerated.

I. **Assay Methodology:**

Methods and Validation:

Similar to the clinical study protocol #013-20-10895, under fasting conditions.

J. **Data Analysis:**

Twenty-six (26) healthy male subjects entered the clinical study but only 24 subjects completed the entire clinical portion of the study. Subject #10 failed to return to the facility for period 2 and subject #13 withdrew during period 2, Day 2 before the morning dose because of cold symptoms. The pharmacokinetic parameters of pentoxifylline, metabolite I and metabolite V were analyzed using an analysis of variance. The statistical differences due to treatments, period, dosing sequence and subjects nested within sequence were evaluated for plasma pentoxifylline, metabolite I and metabolite V concentrations, as well as the following parameters,

AUC_{0-t}, C_{avg}, C_{max}, C_{min}, FLUC (fluctuation at steady state) and T_{max}. The 90% confidence interval and the ratios of the test/reference means were also determined. The pharmacokinetic parameters of the plasma pentoxifylline, metabolite I and metabolite V concentrations for the previous parameters are summarized in Tables #16-24.

Table 16
Mean Plasma Concentrations of Pentoxifylline at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
96	50.79	32.88	51.53	25.58	0.99
96.25	67.99	33.72	68.70	45.32	0.99
96.5	105.60	56.84	106.70	77.96	0.99
97	89.86	49.39	99.56	49.67	0.90
97.5	78.98	37.43	83.27	36.61	0.95
98	75.80	38.20	84.92	43.89	0.89
98.5	69.82	28.24	76.96	40.04	0.91
99	60.89	30.08	69.24	31.13	0.88
99.5	59.06	36.86	66.29	32.98	0.89
100	51.96	29.31	51.34	24.17	1.01
101	41.48	22.07	44.97	23.69	0.92
102	64.71	34.14	68.34	45.20	0.95
103	55.00	30.81	56.17	31.56	0.98
104	43.04	23.73	39.68	23.75	1.08

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 17
Arithmetic and Geometric Mean For Pentoxifylline Pharmacokinetic Parameters at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	501.85	224.98	531.58	252.34	0.94
CAVG	62.73	28.12	66.45	31.54	0.94
CMAX	122.14	55.45	129.43	73.52	0.94
CMIN	32.24	19.45	33.80	21.15	0.95
FLUC	1.52	0.62	1.44	0.48	1.05
*LAUCT	450.46	0.50	473.83	0.52	0.95
*LCAVG	56.31	0.50	59.23	0.52	0.95
*LCMAX	109.53	0.50	111.83	0.57	0.98
*LCMIN	27.04	0.62	28.30	0.62	0.96
*LFLUC	1.42	0.36	1.38	0.29	1.03
TMAX	1.29	0.33	1.58	0.33	0.82

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

Table 18
LSMEANS AND 90% CONFIDENCE INTERVALS For Pentoxifylline at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

	LSMEAN1	LSMEAN2	T/R	LOWCI12	UPPCI12
AUCT	501.85	531.57	0.94	83.69	105.13
CAVG	62.73	66.45	0.94	83.69	105.13
CMAX	122.14	129.42	0.94	82.32	106.42
CMIN	32.24	33.80	0.95	77.77	113.03
FLUC	1.52	1.44	1.06	91.51	119.21
***LAUCT**	**450.46**	**473.83**	**0.95**	**85.09**	**106.22**
*LCAVG	56.31	59.23	0.95	85.09	106.22
***LCMAX**	**109.53**	**111.83**	**0.98**	**87.45**	**109.70**
*LCMIN	27.04	28.30	0.96	80.79	113.01
*LFLUC	1.42	1.38	1.03	91.35	115.86

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.

RLSM12=T/R ratios (under non-fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the LSMEAN (antilog of the means of the logs).
AUCT= $AUCT_{96-104}$
CAVG= AUCT/8
CMIN= minimum conc. from time range 96-104 hours
FLUC= [CMAX -CMIN]/CMIN

1. The mean plasma pentoxifylline levels for the test product and reference products reached maximum level of concentrations around 96.5 hours (Table #16 and the attached Figure #7).

2. The 90% confidence intervals for the LSMEAN log-transformed values for AUC_{96-104} and C_{max} were within the acceptable range of 80-125% (Table #18). The 90% confidence intervals for the geometric log-transformed values for AUC_{96-104} and C_{max} were also within the acceptable range of 80-125% (Table #17).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters C_{max}.

   For the AUC_{96-104}, there were no significant sequence or treatment effects of the test and reference drug treatments. However, there was significant period effect (p less than 0.05) for the log-transformed pharmacokinetic parameters AUC_{96-104}.

3. The LSMEAN value for fluctuation of the test product was similar to the reference product fluctuation product value (Table #18).

Table 19
Mean Plasma Concentrations of Metabolite I at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
96	335.19	182.65	325.00	181.20	1.03
96.25	288.80	144.58	284.08	144.81	1.02
96.5	363.85	167.65	361.12	197.18	1.01
97	441.67	204.42	441.21	207.56	1.00
97.5	447.17	205.70	467.92	217.72	0.96
98	439.40	193.95	462.71	207.00	0.95
98.5	426.79	189.48	445.63	187.81	0.96
99	402.75	187.14	426.21	188.22	0.94
99.5	369.08	190.28	394.00	177.45	0.94
100	337.11	186.31	361.42	156.86	0.93
101	295.60	172.03	304.25	142.29	0.97
102	272.17	149.67	274.43	161.29	0.99
103	231.55	134.23	230.13	133.03	1.01
104	207.00	120.63	199.83	119.73	1.04

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 20
Arithmetic and Geometric Mean for Metabolite I Pharmacokinetic Parameters at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	2669.65	1304.23	2745.70	1260.37	0.97
CAVG	333.71	163.03	343.21	157.55	0.97
CMAX	470.83	206.35	497.71	215.29	0.95
CMIN	183.95	96.05	190.83	116.20	0.96
FLUC	0.90	0.18	0.93	0.23	0.96
*LAUCT	2375.89	0.51	2479.77	0.48	0.96
*LCAVG	296.99	0.51	309.97	0.48	0.96
*LCMAX	425.34	0.48	452.45	0.47	0.94
*LCMIN	158.10	0.60	160.85	0.62	0.98
*LFLUC	0.89	0.20	0.91	0.26	0.98
TMAX	1.91	0.74	1.80	0.78	1.06

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

Table 21
LSMEANS AND 90% CONFIDENCE INTERVALS
For Metabolite I at Steady-State (Day 5) in
24 Subjects After 400 mg of Pentoxifylline ER Tablet
every 8 hours for 13 doses
Unit: ng/mL

	LSMEAN1	LSMEAN2	T/R	LOWCI12	UPPCI12
AUCT	2669.65	2745.70	0.97	89.64	104.82
CAVG	333.71	343.21	0.97	89.64	104.82
CMAX	470.83	497.71	0.95	87.31	101.90
CMIN	183.95	190.83	0.96	82.53	110.26
FLUC	0.90	0.93	0.97	86.33	106.58
***LAUCT**	**2375.89**	**2479.77**	**0.96**	**86.53**	**106.09**
*LCAVG	296.99	309.97	0.96	86.53	106.09
***LCMAX**	**425.34**	**452.45**	**0.94**	**85.94**	**102.83**
*LCMIN	158.10	160.85	0.98	84.58	114.22
*LFLUC	0.89	0.91	0.98	87.87	108.43

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.
RLSM12=T/R ratios (under non-fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the LSMEAN (antilog of the means of the logs).
AUCT= $AUCT_{96-104}$
CAVG= AUCT/8
CMIN= minimum conc. from time range 96-104 hours
FLUC= [CMAX -CMIN]/CMIN

1. The mean plasma metabolite I levels for the test product and reference products reached maximum level of concentrations around 97.5 hours (Table #19 and the attached Figure #8).

2. The 90% confidence intervals for the LSMEAN log-transformed values for AUC_{96-104} and C_{max} were within the acceptable range of 80-125% (Table #21). The 90% confidence intervals for the geometric log-transformed values for AUC_{96-104} and C_{max} were also within the acceptable range of 80-125% (Table #20).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters C_{max}.

For the AUC_{96-104}, there were no significant period or treatment effects of the test and reference drug treatments. However, there was significant sequence effect (p less than 0.05) for the log-transformed pharmacokinetic parameters AUC_{96-104}.

3. The LSMEAN value for fluctuation of the test product was similar to the reference product fluctuation mean value (Table #21).

Table 22
Mean Plasma Concentrations of Metabolite V
at Steady-State (Day-5) in 24 Subjects
After 400 mg of Pentoxifylline ER Tablet
every 8 hours for 13 doses
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
96	770.08	323.94	778.63	329.67	0.99
96.25	648.79	157.08	661.21	208.21	0.98
96.5	841.33	145.83	850.38	240.54	0.99
97	1011.13	197.93	1065.88	286.04	0.95
97.5	976.42	221.05	1042.83	282.48	0.94
98	940.50	239.50	986.13	251.15	0.95
98.5	892.92	220.51	956.42	260.85	0.93
99	843.21	198.64	896.04	234.43	0.94
99.5	765.50	183.95	824.21	210.04	0.93
100	708.71	187.08	747.63	192.31	0.95
101	608.92	173.41	655.29	171.55	0.93
102	598.38	183.22	613.88	185.90	0.97
103	526.21	180.40	534.75	140.96	0.98
104	460.04	138.82	443.88	127.90	1.04

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 23
Arithmetic and Geometric Mean for Metabolite V Pharmacokinetic Parameters at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	5784.00	1311.92	6053.88	1341.25	0.96
CAVG	723.00	163.99	756.73	167.66	0.96
CMAX	1041.83	217.66	1123.42	255.98	0.93
CMIN	426.04	133.95	421.33	114.78	1.01
FLUC	0.87	0.21	0.94	0.24	0.93
*LAUCT	5651.34	0.22	5872.83	0.27	0.96
*LCAVG	706.42	0.22	734.10	0.27	0.96
*LCMAX	1022.46	0.19	1093.15	0.25	0.94
*LCMIN	405.13	0.33	400.33	0.37	1.01
*LFLUC	0.85	0.24	0.92	0.25	0.93
TMAX	1.29	0.46	1.55	0.92	0.83

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

Table 24
LSMEANS AND 90% CONFIDENCE INTERVALS For Metabolite V at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

PARAMETER	LSMEAN1	LSMEAN2	T/R	LOWCI12	UPPCI12
AUCT	5784.00	6053.88	0.96	88.77	102.32
CAVG	723.00	756.73	0.96	88.77	102.32
CMAX	1041.83	1123.42	0.93	84.72	100.76
CMIN	426.04	421.33	1.01	91.14	111.10
FLUC	0.87	0.94	0.93	82.61	102.97
***LAUCT**	**5651.34**	**5872.83**	**0.96**	**88.95**	**104.10**
*LCAVG	706.42	734.10	0.96	88.95	104.10
***LCMAX**	**1022.46**	**1093.15**	**0.94**	**86.33**	**101.33**
*LCMIN	405.13	400.33	1.01	88.84	115.27
*LFLUC	0.85	0.92	0.92	83.89	103.09

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.

RLSM12=T/R ratios (under non-fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML, TMAX=HR
* The values represent the antilog of the means of the logs.
AUCT= $AUCT_{96-104}$
CAVG= AUCT/8
CMIN= minimum conc. from time range 96-104 hours
FLUC= [CMAX - CMIN]/CMIN

1. The mean plasma metabolite I levels for the test product and reference products reached maximum level of concentrations around 97 hours (Table #22 and the attached Figure #9).

2. The 90% confidence intervals for the LSMEAN log-transformed values for AUC_{96-104} and C_{max} were within the acceptable range of 80-125% (Table #24). The 90% confidence intervals for the geometric log-transformed values for AUC_{96-104} and C_{max} were also within the acceptable range of 80-125% (Table #22).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC_{96-104} and C_{max}.

3. The LSMEAN mean value for fluctuation of the test product was similar to the reference product fluctuation mean value (Table #24).

V. FORMULATION

ESI Lederle's formulation of its drug product, Pentoxifylline 400 mg Extended Release Tablets is summarized in Table #25.

The reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets contain 400 mg of the active drug (Pentoxifylline) and the following inactive ingredients: benzyl alcohol NF, D&C Red No. 27 aluminum lake or FD&C Red No. 3, hydroxypropyl methylcellulose USP, magnesium stearate NF, polyethylene glycol NF, povidone USP, talc USP, titanium dioxide USP, and other ingredients in a controlled-release formulation.

Table 25
Formulation of the Test product[1]

Ingredients	Quantity/ Batch	mg/Tablet	%W/W
Pentoxifylline[2]		400.000	65.043
Talc USP[2]			
Polyethylene Glycol 6000 NF			
White			
Magnesium Stearate NF			
Povidone USP			
Hydroxyethyl Cellulose			
Purified Water USP[3,5]			
Total		614.980	100.00

[1]NOT FOR RELEASE UNDER FOI

VI. IN VITRO DISSOLUTION TESTING

The firm has submitted comparative dissolution testing data for its drug product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets.

Method:	USP 23 apparatus II (Paddle) at 75 rpm
Medium:	Deaerated Purified Water (Pentoxifylline is soluble in water, 77 mg/mL)
Temperature:	37°C ± 0.5°C
Volume:	900 mL
Reporting Intervals:	1.0, 6.0, 10.0 and 20.0 hours
No. Units Tested:	12 Tablets
Reference product:	Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Test Lot#:	93250-0100
Reference Lot#:	0781255

The firm's specification to control the dissolution rate are as follows (The specifications were taken from vol. A1.15, pages 5178-5183):

Time (Hour)	%Released
1	NLT
6	NLT
10	NLT
20	NLT

The dissolution testing method and specification for the reference listed product,Hoechst-Roussel's Trental® 400 mg Extended Release Tablets (NDA #18631) as follows:

a. The dissolution testing conducted in 900 mL of water using USP appratus 2 (Paddle) at 100 rpm.

b. Specification Limits

Time (Hour)	%Released
1	NLT
4	
8	NLT
12	NLT

Table #26 In Vitro Dissolution Testing

Drug (Generic Name):Pentoxifylline
Dose Strength: 400 mg Extended Release Tablets
ANDA No. : 74-877
Firm:ESI Lederle
Submission Date: March 28, 1996
File Name: 74877sd.396

I. Conditions for Dissolution Testing:

USP23 Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium:Deaerated Purified Water
Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product: Pentoxifylline Lot #93250-0100 Strength (mg) 400 mg			Reference Product:Trental® Lot #0781255 Strength (mg) 400 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
1	15		9.6	14		2.8
6	45		4.4	45		2.8
10	63		4.1	64		2.9
20	94		3.3	97		3.3

Table #27 In Vitro Dissolution Testing

Drug (Generic Name):Pentoxifylline
Dose Strength: 400 mg Extended Release Tablets
ANDA No. : 74-877
Firm:ESI Lederle
Submission Date: March 28, 1996
File Name: 74877sd.396

I. Conditions for Dissolution Testing:

USP23 Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: HCl, pH 1.2
Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product: Pentoxifylline Lot #93250-0100 Strength (mg) 400 mg			Reference Product:Trental® Lot #0781255 Strength (mg) 400 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
1	16		11	14		2.1
2	23		7.7	22		2.2
4	35		5.4	34		2.0
6	45		4.3	45		2.2
8	54		3.4	55		2.0
10	63		3.3	64		1.9
12	71		3.0	72		2.0
14	78		2.5	80		2.0
16	85		2.1	87		2.0
18	91		1.5	94		2.4
20	95		1.2	100		2.6
22	99		1.3	103		1.7
24	101*		1.7	104		1.3

* Represent the mean for 6 tablets.

Table #28 In Vitro Dissolution Testing

Drug (Generic Name):Pentoxifylline
Dose Strength: 400 mg Extended Release Tablets
ANDA No. : 74-877
Firm:ESI Lederle
Submission Date: March 28, 1996
File Name: 74877sd.396

I. Conditions for Dissolution Testing:

USP23 Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: HCl, pH 4.5
Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product: Pentoxifylline Lot #93250-0100 Strength (mg) 400 mg			Reference Product:Trental® Lot #0781255 Strength (mg) 400 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
1	15		5.0	14		5.1
2	23		4.3	22		3.6
4	35		3.6	34		3.6
6	45		3.4	44		4.0
8	54		3.3	53		3.7
10	63		3.7	62		3.5
12	70		3.4	70		3.9
14	78		3.3	77		3.8
16	84		3.3	84		3.5
18	90		3.0	89		3.5
20	95		2.4	95		3.6
22	99		1.9	98		3.1
24	101		1.5	101		2.5

Table #29 In Vitro Dissolution Testing

Drug (Generic Name):Pentoxifylline
Dose Strength: 400 mg Extended Release Tablets
ANDA No. : 74-877
Firm:ESI Lederle
Submission Date: March 28, 1996
File Name: 74877sd.396

I. Conditions for Dissolution Testing:

USP23 Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: Phosphate Buffer, pH 6.0
Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product: Pentoxifylline Lot #93250-0100 Strength (mg) 400 mg			Reference Product:Trental® Lot #0781255 Strength (mg) 400 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
1	17		9.1	14		7.5
2	24		8.3	22		4.1
4	35		6.3	34		3.6
6	45		6.5	44		3.4
8	54		6.2	54		2.8
10	62		6.1	62		3.0
12	69		7.6	70		3.0
14	77		5.9	77		2.8
16	83		5.8	84		2.8
18	88		5.4	90		2.9
20	93		5.2	96*		3.2
22	97		4.6	100**		2.8
24	100		3.5	103**		2.3

* Represents the mean of 11 tablets.
** Represents the mean of 10 tablets.

Table #30 In Vitro Dissolution Testing

Drug (Generic Name):Pentoxifylline
Dose Strength: 400 mg Extended Release Tablets
ANDA No. : 74-877
Firm:ESI Lederle
Submission Date: March 28, 1996
File Name: 74877sd.396

I. Conditions for Dissolution Testing:

USP23 Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: Phosphate Buffer, pH 7.5
Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product: Pentoxifylline Lot #93250-0100 Strength (mg) 400 mg			Reference Product:Trental® Lot #0781255 Strength (mg) 400 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
1	13		5.1	13		2.2
2	20		3.7	20		2.9
4	31		3.9	32		2.6
6	40		3.4	42		2.9
8	49		3.4	51		2.7
10	57		3.4	59		2.8
12	64		3.2	67		2.8
14	71		3.1	74		2.9
16	78		3.0	80		2.7
18	83		2.8	86		3.0
20	88		2.7	92		3.1
22	93		2.4	96		2.9
24	96		1.9	100		2.9

Comments on the Dissolution Data:
The dissolution results for the test and reference products under different dissolution media using USP 23 apparatus 2 (Paddle) at 75 rpm indicated that the dissolution profile for the test and reference products are comparable.

VII. COMMENTS

1. Under Fasting Conditions:
The firm's single-dose bioequivalence study under fasting conditions demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within of the acceptable range of 80-125% for Pentoxifylline, Metabolite I and Metabolite V. However, the ANDA has been found incomplete by the Division of Bioequivalence for the reasons cited in the deficiency section (see below).

2. Under Non-Fasting Conditions:
The firm's single-dose bioequivalence study #013-21-10896 under non-fasting conditions demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets are bioequivalent. The ratios of the test LSMEAN to the reference LSMEAN for AUC0-t, AUC_{0-inf} and C_{max} are within the acceptable range of 0.8-1.2 for Pentoxifylline, Metabolite I and Metabolite V. However, the ANDA has been found incomplete by the Division of Bioequivalence for the reasons cited in the deficiency section (see below).

3. Under Multiple-Dosing Study:
The firm's multiple-dose bioequivalence study #013-22-10897 demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t} and C_{max} were within the acceptable range of 80-125%. However, the ANDA has been found incomplete by the Division of Bioequivalence for the reasons cited in the deficiency section (see below).

4. The dissolution testing conducted by ESI Lederle, on its the test product, Pentoxifylline 400 mg Extended Release Tablets (Lot #93250-0100) is acceptable. The dissolution testing should be conducted in 900 mL of deaerated purified water at 37°C using USP 23 appratus 2 (Paddle) at 75 rpm. Based on the submitted data the following tentative specification are recommended:

1	hour	NLT
6	hours	NLT
10	hours	NLT
20	hours	NLT

However, the ANDA has been found incomplete by the Division of

Bioequivalence for the reasons cited in the deficiency section (see below).

VIII. DEFICIENCIES:

1. There are a number of samples (all samples from the single-dose study, under fasting conditions) that were reported by the firm as 'not analytically valid assay'.

   These samples are the following:
   For Pentoxifylline: subjects #11, 26, 30, 31, 35, 38 and 39
   For Metabolite I: subjects #14, 17 and 30
   For Metabolite V: subject #30
   In addition to other samples listed on Table A, page #186, Vol. C1.2

   The firm is requested to respond to the following itms:

   a. An explanation for the statement 'not analytically valid assay'.

   b. The reason(s) to eliminate subjects (#11, 26, 30, 31, 35, 38 and 39) and samples (mentioned in Table A) from the final statistical analysis.

   c. Provide the actual raw values for the missing subjects (#11, 26, 30, 31, 35, 38 and 39) and samples (mentioned in Table A).

   d. Provide the raw data (under fasting conditions only) for the plasma levels and all pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{1/2}$ and K_{el}) for all subjects (including the missing subjects and samples) in the study.

   e. Please submit the raw data (under fasting conditions only) on a floppy diskette (ASCII format) for plasma levels and all pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{1/2}$ and K_{el}) for all subjects. The diskette should contain the following variables (in the same order, if possible): subject number, period, sequence, treatment, C_1-C_{last}, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{1/2}$ and K_{el} in order for the reviewer to run his own SAS-PROC GLM statistical package.

2. On page #186, line #1, Volume #C1.2, the firm provided the following statement 'All analytical runs did not meet acceptance criteria for all analytes'. Please provide a clarification of this statement .

IX. RECOMMENDATION

The three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple dose) conducted by ESI Lederle comparing its test product Pentoxifylline 400 mg Extended Release Tablets to the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets have been found **incomplete** by the Division of Bioequivalence for the deficiencies cited above (#1 and 2).

The firm should be informed of the deficiencies and recommendations.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATR _____ 10/23/96

Concur: Not needed per 10/17/95 memo III A Date: _____
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA#74-877, original, HFD-630 (OGD), HFD-604 (Hare), HFD-658 (Mhatre, Wahba), Drug File
ZZWahba/091196/101796/file#74877sd.396

Figure 1: Mean Pentoxifylline Plasma Levels

#013 – 20 – 10895

ANDA #74-877

N = 34

Under Fasting conditions

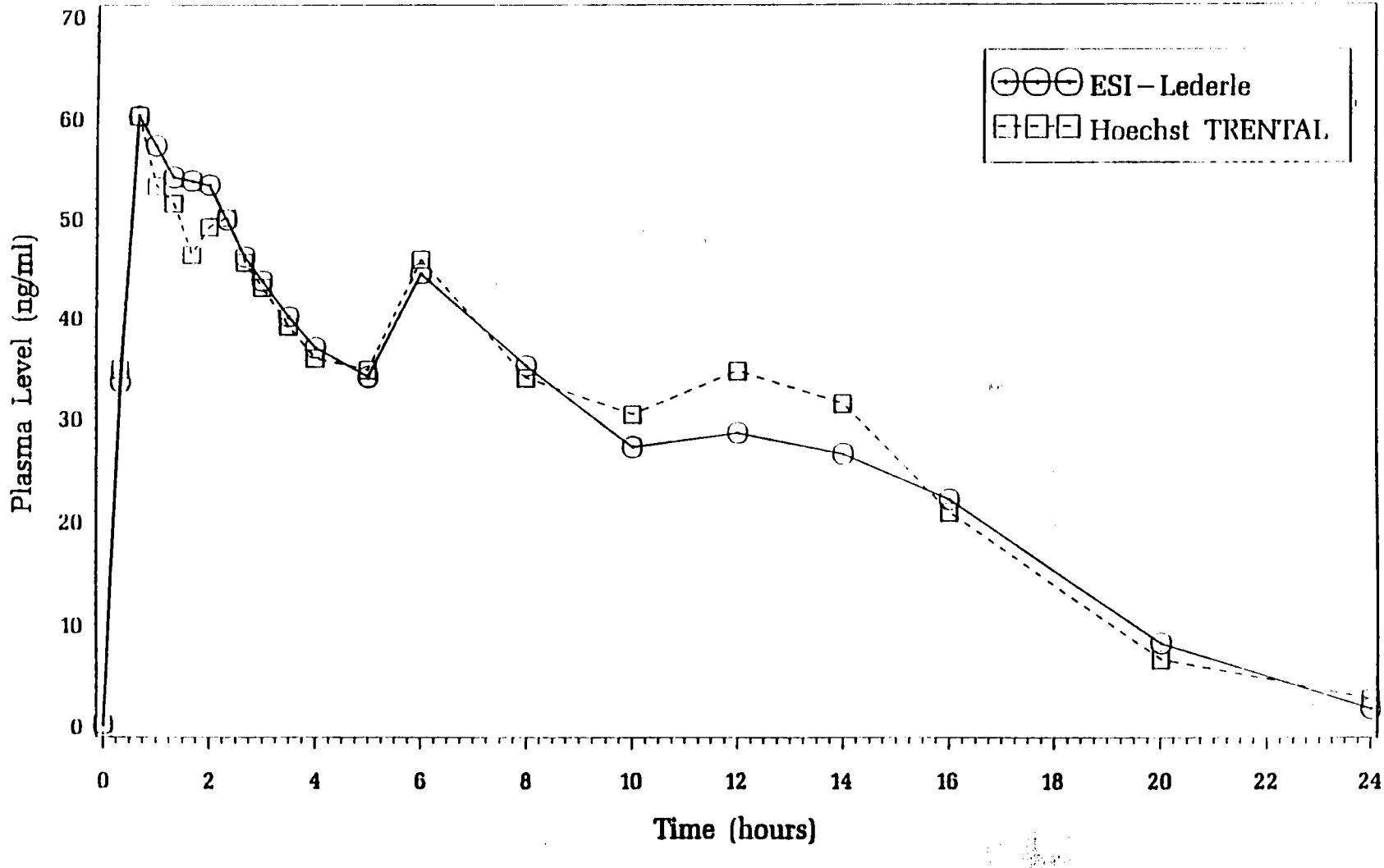


Figure 2: Mean Metabolite I Plasma Levels

#013 – 20 – 10895

ANDA # 74-877 N = 38 Under Fasting Conditions

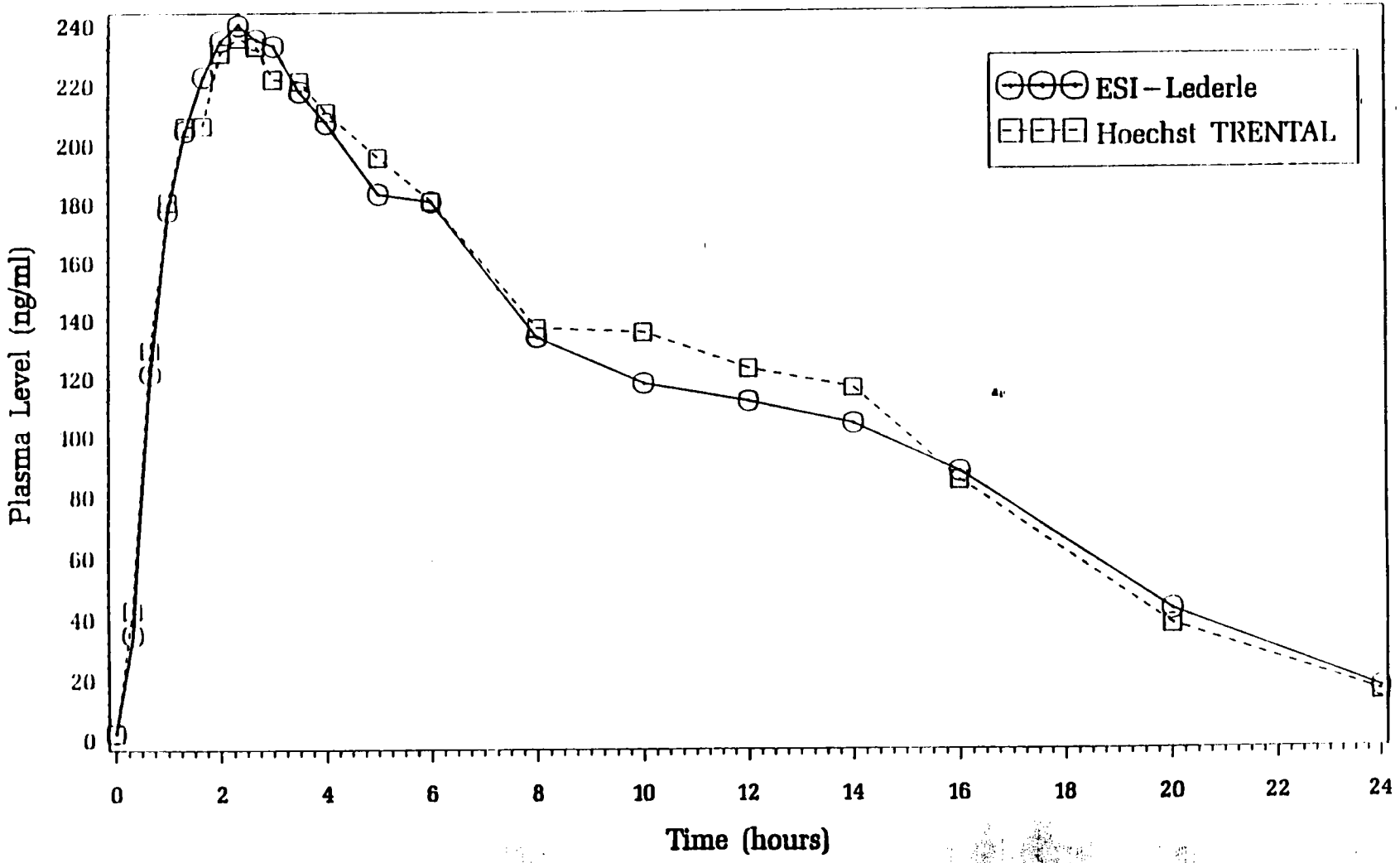


Figure 3: Mean Metabolite V Plasma Levels

#013 – 20 – 10895

ANDA #74-877

N = 40

Under Fasting Conditions

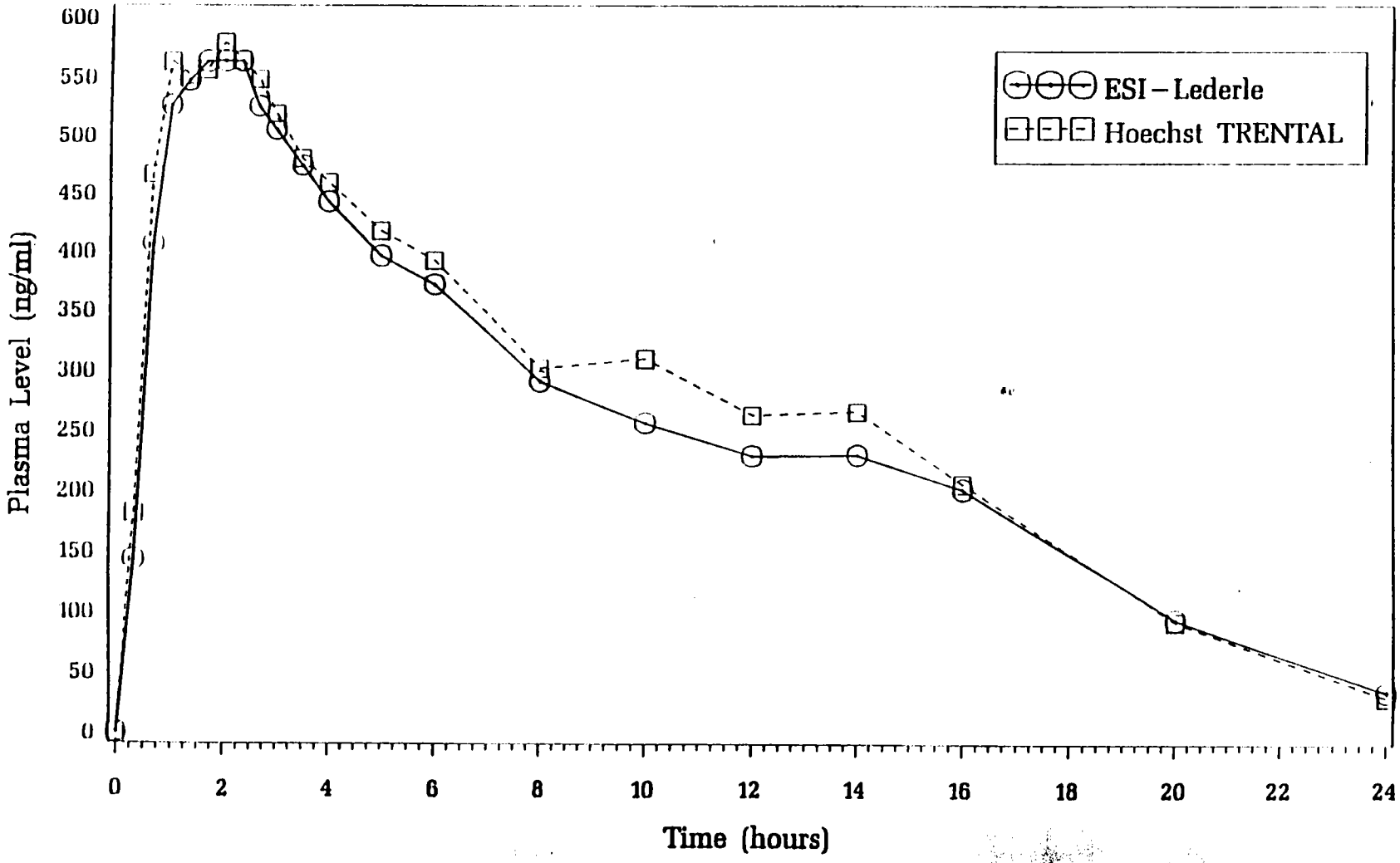
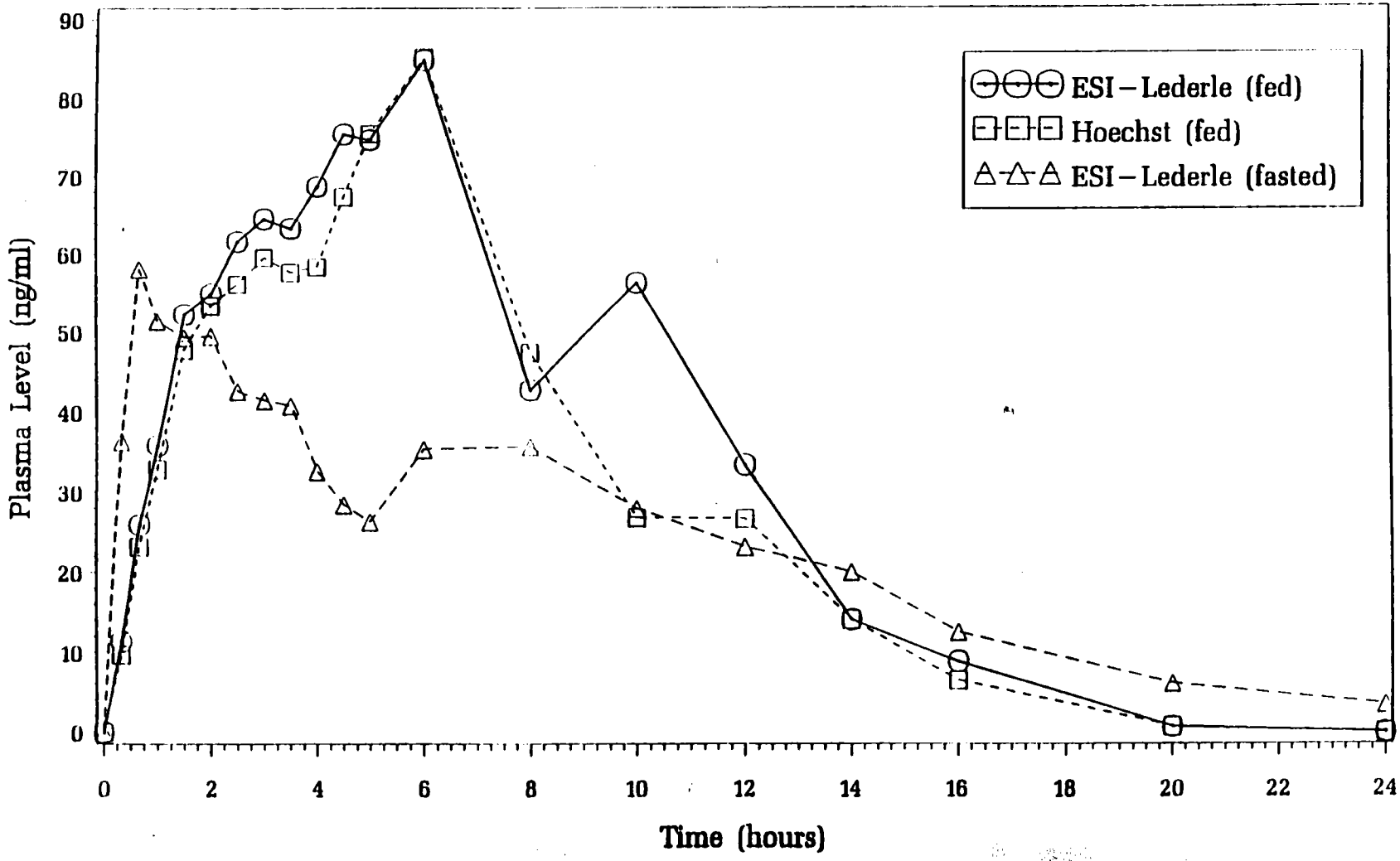


Figure #4 Mean Pentoxifylline Plasma Levels

#013 – 21 – 10896

ANDA#74-877 N = 18 Under Non-fasting Conditions



Figure# 5 Mean Metabolite I Plasma Levels

#013 – 21 – 10896

ANDA # 74-877 N = 18 Under Non-Fasting Conditions

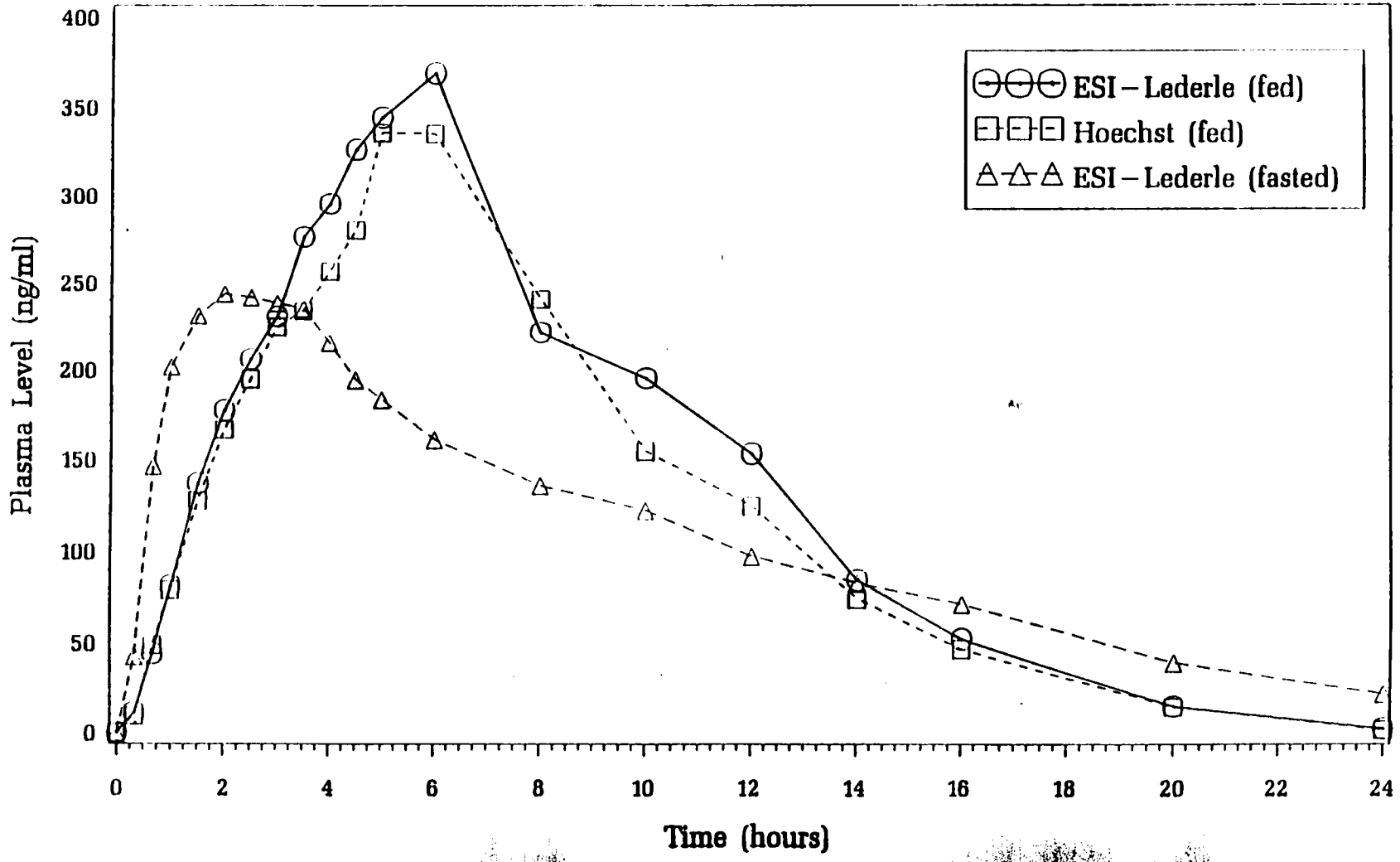
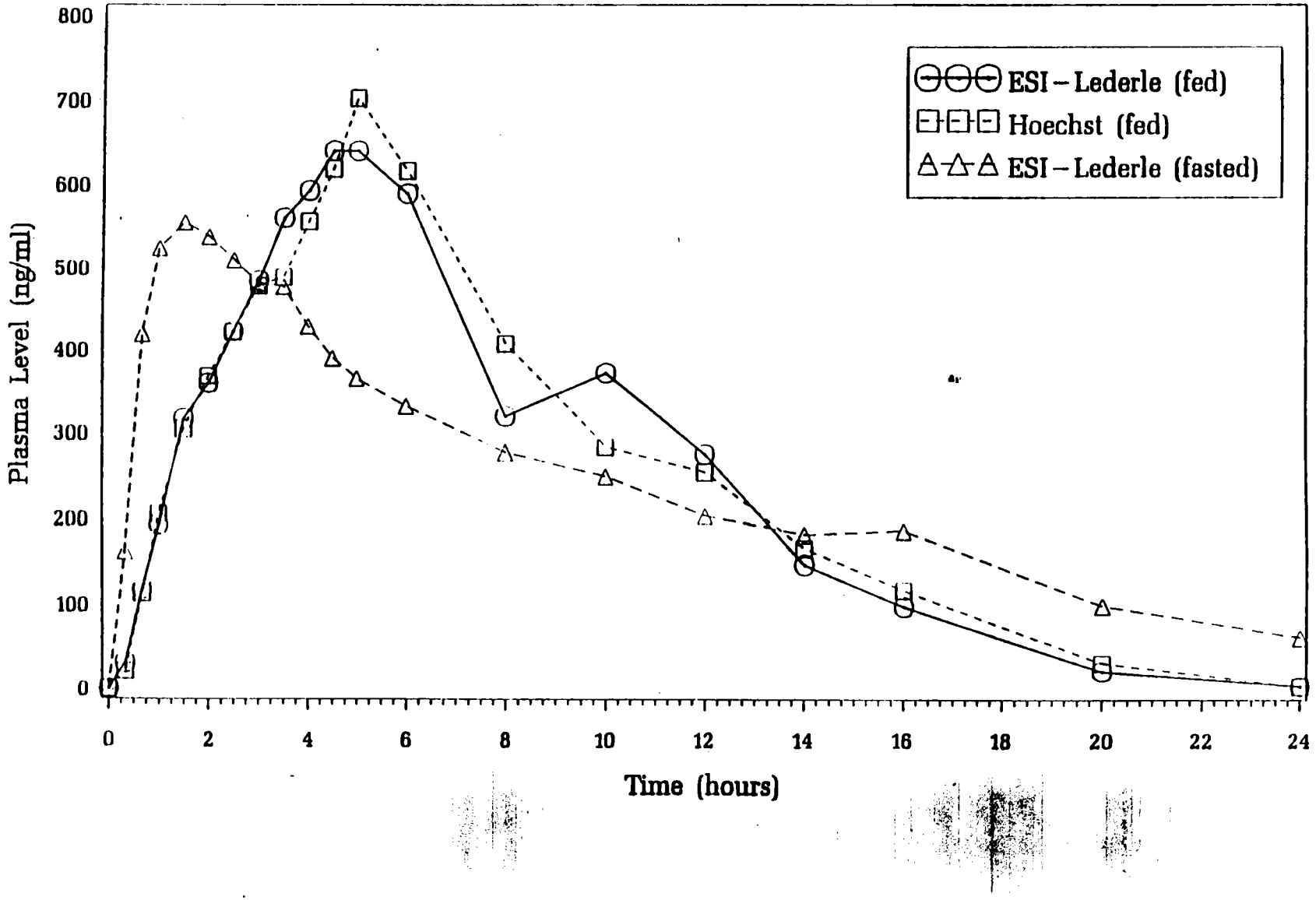


Figure #6 Mean Metabolite V Plasma Levels

#013-21-10896

ANDA#74-877 N = 18

Under Non-Fasting Conditions



Figure#7 Mean Pentoxifylline Plasma Levels
Steady State Interval
#013 – 22 – 10897
N = 24

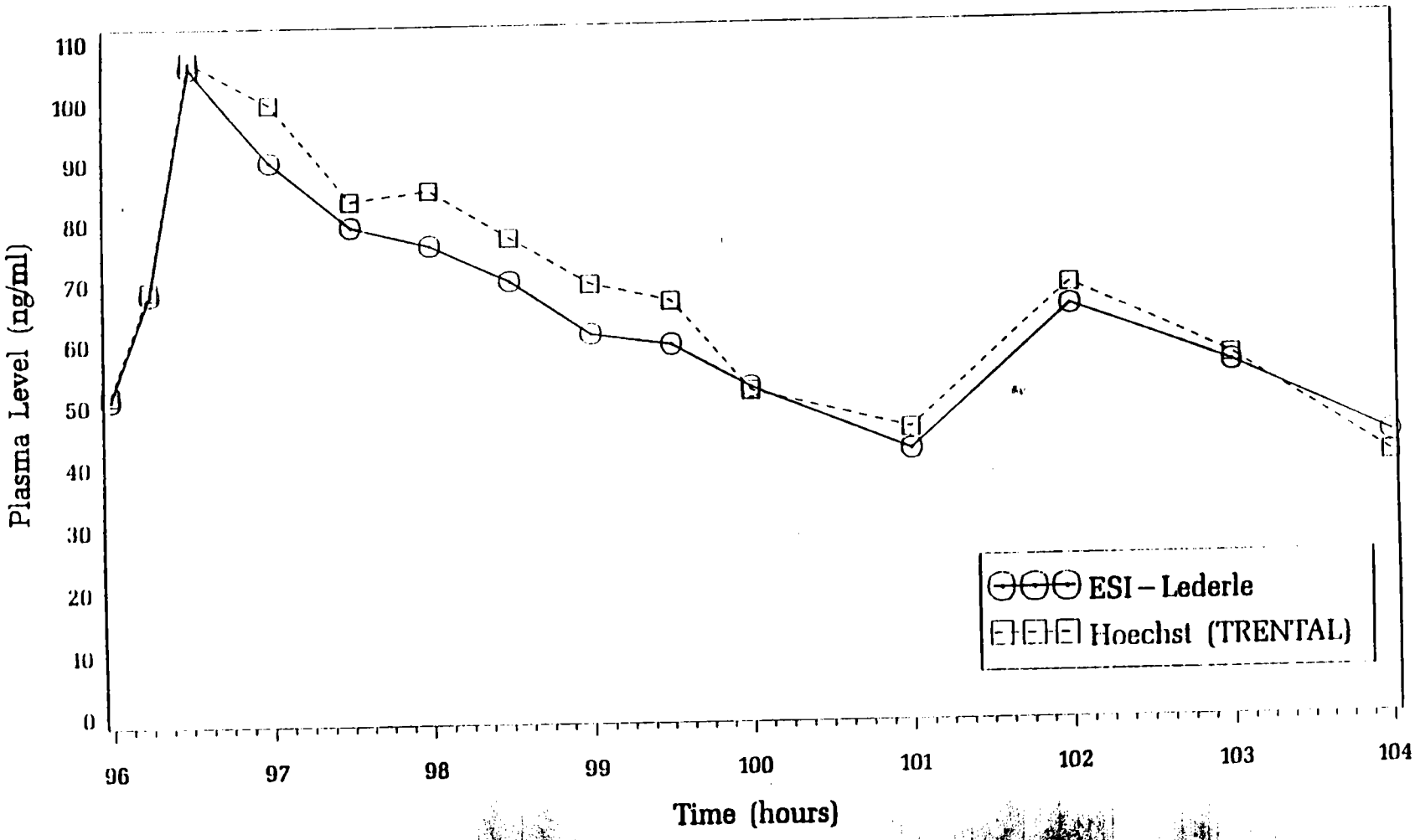


Figure #8. Mean Metabolite I Plasma Levels
Steady State Interval
#013 – 22 – 10897
N = 24

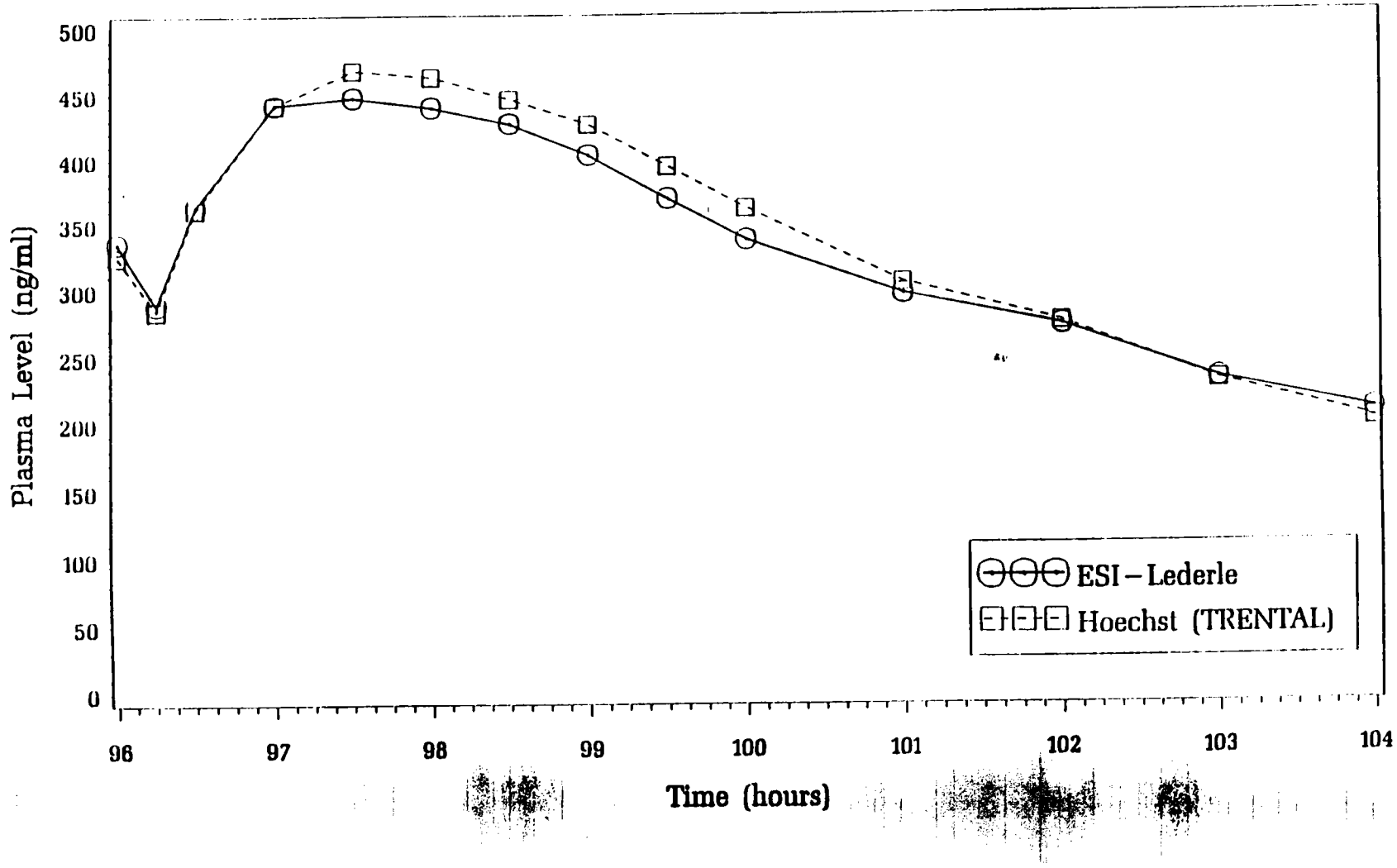
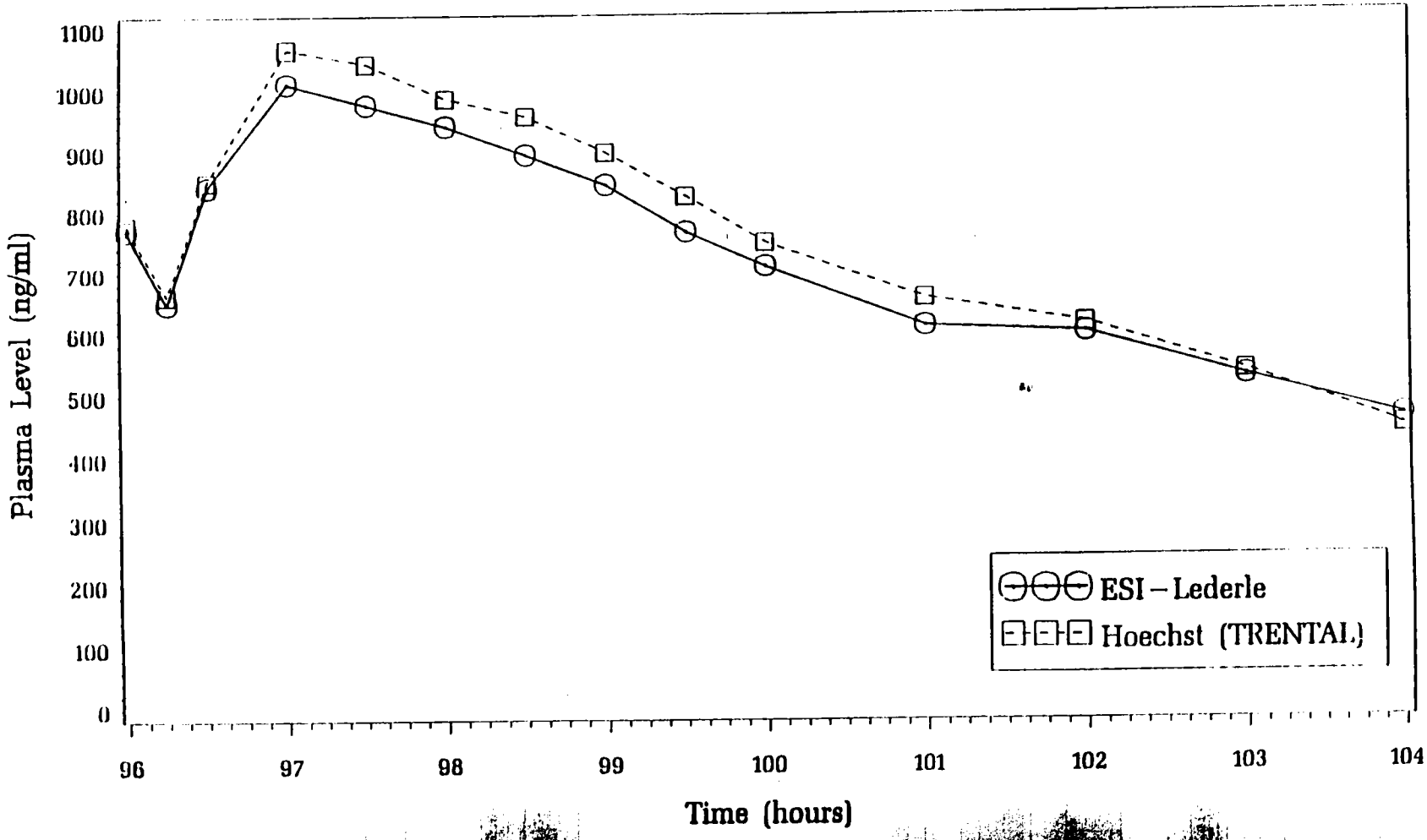


Figure #9. Mean Metabolite V Plasma Levels
Steady State Interval
#013 – 22 – 10897
N = 24



JUN 30 1997

Pentoxifylline
400 mg Extended Release Tablets
ANDA #74-877
Reviewer: Z.Z. Wahba
File #74877a.d96

ESI Lederle
Pearl River, NY
Submission Date:
December 04, 1996

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY AND DISSOLUTION DATA (Dated October 23, 1996)

BACKGROUND

The firm had previously submitted three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple-dose) comparing its test drug product, ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets to the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets.

The submission was reviewed and was found to be incomplete by the Division of Bioequivalence (the review dated October 23, 1996, ANDA #74-877) due to problems cited in the deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Deficiency Comment #1

There are a number of samples (all samples from the single-dose study, under fasting conditions) that were reported by the firm as "no analytically valid assay".

These samples are the following:
For Pentoxifylline: subjects #11, 26, 30, 31, 35, 38 and 39
For Metabolite I: subjects #14, 17 and 30
For Metabolite V: subject #30
In addition to other samples listed on Table A, page #186, Vol. C1.2

The firm is requested to respond to the following items:

a. An explanation for the statement "no analytically valid assay".

b. The reason(s) for eliminating subjects (#11, 26, 30, 31, 35, 38 and 39) and samples (mentioned in Table A) from the final statistical analysis.

c. Provide the actual raw values for the missing subjects

(#11, 26, 30, 31, 35, 38 and 39) and samples (mentioned in Table A).

d. Provide the raw data (under fasting conditions only) for the plasma levels and all pharmacokinetic parameters (AUCt, AUCi, Cmax, Tmax, T1/2 and Kel) for all subjects (including the missing subjects and samples)in the study.

e. Please submit the raw data (under fasting conditions only) on a floppy diskette (ASCII format) for plasma levels and all pharmacokinetic parameters (AUCt, AUCi, Cmax, Tmax, T1/2 and Kel) for all subjects. The diskette should contain the following variables (in the same order, if possible): subject number, period, sequence, treatment, C1-Clast,AUCt, AUCi, Cmax, Tmax, T1/2 and Kel in order for the reviewer to run his own SAS-PROC GLM statistical package.

The firm's response to comment #1a

The firm's response to comment #1a is acceptable.

The firm's response to comment #1b

The firm's response to comment #1b is acceptable.

The firm's response to comment #1c

As described in reply #1a, no reportable results were obtained for these individual samples.

The firm's response to comment #1c is acceptable.

The firm's response to comment #1d

The firm's response to comment #1d is acceptable.

The firm's response to Comment #1e

A diskette that contains the requested information was provided.

The firm's response to comment #1e is acceptable.

In Vivo BE Study and Statistical Analysis (Under Fasting Conditions)

Forty-two (42) subjects were enrolled in this two-treatment crossover study. Subject #28 voluntarily withdrew after completing period I and before period II. Data from the first forty subjects (#1-27 and 29-41) to complete the study were reanalyzed. All subjects received a single oral dose of 400 mg pentoxifylline on two occasions separated by one week.

The pharmacokinetic parameters of pentoxifylline, metabolite I and metabolite V were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters of the level of plasma concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the tables below:

Table 1
Mean Plasma Concentrations of Pentoxifylline in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions
Unit: ng/mL
(Test lot #93250-0100, Ref. Lot #0781255)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	35.56	39.14	40.46	33.29	0.88
0.67	65.43	44.66	65.07	30.96	1.01
1	62.88	36.09	62.32	31.16	1.01
1.33	56.67	32.28	60.61	34.10	0.93
1.67	57.36	31.42	53.52	25.75	1.07
2	55.50	32.42	52.37	29.25	1.06
2.33	52.77	31.55	52.40	28.25	1.01
2.67	48.85	30.25	45.20	25.16	1.08
3	44.70	24.15	44.96	23.85	0.99
3.5	41.66	22.04	40.50	23.45	1.03
4	39.46	25.39	36.21	20.24	1.09
5	33.31	18.06	32.38	18.59	1.03
6	42.57	27.09	45.75	26.66	0.93
8	34.89	23.57	33.88	20.30	1.03
10	28.43	17.96	32.02	15.96	0.89
12	29.54	16.18	34.46	20.41	0.86
14	27.78	20.51	33.49	21.78	0.83
16	22.01	16.65	22.83	17.26	0.96
20	8.00	10.71	8.04	10.72	0.99
24	1.54	3.96	2.42	6.24	0.63

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 2
Arithmetic Mean
Pentoxifylline Pharmacokinetic Parameters
in 40 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet
under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
*AUCI	727.82	313.92	804.78	374.14	0.90
AUCT	633.03	329.18	666.63	343.70	0.95
CMAX	84.82	45.13	83.55	37.20	1.02
KE	0.26	0.15	0.22	0.12	1.19
THALF	3.49	1.97	4.10	1.96	0.85
TMAX	2.18	3.19	1.61	1.82	1.35

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* N=19

Table 3
LSMEANS AND 90% CONFIDENCE INTERVALS
in 40 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
*LAUCI	655.10	696.34	0.94	86.38	102.46
LAUCT	552.63	585.97	0.94	86.50	102.82
LCMAX	73.39	76.79	0.96	87.16	104.80

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
T/R= Test/Ref. ratios (under fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* N=19

1. The mean plasma pentoxifylline levels reached a maximum level of concentration around 0.67 hour (Table #1 and the attached Figure #1).

2. The 90% confidence intervals based on the LSMEAN for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3). The T/R mean ratios of the LSMEAN for log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25 (Table #3).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-

transformed pharmacokinetic parameters AUCt, AUCi and Cmax.

3. The average mean for T1/2, Tmax and Kel values were 15% lower, 35% higher and 19% higher, respectively, for the test product than for the reference product (Table #2).

Note: There were three subjects (#3, 13 and 39) that showed Cmax values for pentoxifylline at the first time point (0.33 hour). The following table shows the Lsmean and 90% confidence interval values for all subjects excluding subjects #3, 13 and 39.

Table 4
LSMEANS AND 90% CONFIDENCE INTERVALS
in 37 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
*LAUCI	632.67	682.72	0.93	85.15	100.85
LAUCT	530.96	574.45	0.92	84.36	101.28
LCMAX	70.04	75.47	0.93	84.39	102.07

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
T/R= Test/Ref. ratios (under fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* N=18

Results and Conclusion: Tables #3 and #4 obtained from the statistical analysis of all subject (40 subjects) and the 37 subjects (excluding subjects 3, 13 and 39), respectively, show that there is no difference in the outcome if the three subjects (#3, 13 and 39) either included or excluded from the statistical analysis. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax for the data either including or excluding the three subjects were within the acceptable range of 80-125%.

Table 5
Mean Plasma Concentrations of Metabolite I in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions (Unit: ng/mL) (Test lot #93250-0100, Ref. Lot #0781255)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	32.55	36.84	43.31	42.10	0.75
0.67	120.90	75.52	131.98	73.63	0.92
1	184.20	102.29	187.83	93.26	0.98
1.33	214.01	119.61	221.71	103.22	0.97
1.67	229.42	122.02	234.11	103.21	0.98
2	239.84	120.93	237.98	100.39	1.01
2.33	247.24	129.03	241.42	115.72	1.02
2.67	242.02	127.09	242.88	120.86	1.00
3	232.06	117.15	239.37	117.21	0.97
3.5	221.88	105.82	227.52	120.75	0.98
4	213.10	105.39	215.68	116.83	0.99
5	191.14	98.47	200.09	108.01	0.96
6	182.55	93.61	188.19	105.22	0.97
8	136.21	79.15	138.96	78.81	0.98
10	123.35	73.66	139.92	80.52	0.88
12	114.54	76.30	122.72	71.60	0.93
14	98.20	57.25	116.93	69.80	0.84
16	81.88	58.97	85.20	52.43	0.96
20	40.55	38.02	37.43	36.58	1.08
24	13.34	24.24	11.93	22.18	1.12

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 6
Arithmetic Mean Metabolite I Pharmacokinetic Parameters in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
*AUCI	2932.47	1569.90	3026.14	1485.68	0.97
AUCT	2684.57	1404.69	2807.79	1418.22	0.96
CMAX	267.43	135.56	274.38	126.71	0.97
KE	0.26	0.15	0.24	0.12	1.08
THALF	3.61	2.09	3.69	1.89	0.98
TMAX	2.72	2.07	3.13	2.44	0.87

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* N=34

Table 7
LSMEANS AND 90% CONFIDENCE INTERVALS (Metabolite I) in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	2508.22	2646.62	0.95	89.40	100.46
LAUCT	2350.56	2491.87	0.94	89.01	99.96
LCMAX	235.20	248.51	0.95	89.95	99.58

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
T/R= Test/Ref. ratios (under fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

1. The mean plasma metabolite I levels reached a maximum level of concentration around 2.33-2.67 hours (Table #5 and the attached Figure #2).

2. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #7). The T/R mean ratios of the LSMEAN for log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25 (Table #6).

   There were no significant period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCt, AUCi and Cmax.

   For the AUCt and AUCi, there were no significant sequence effect of the test and reference drug treatments. However, there was a significant sequence effect (p less than 0.05) for the log-transformed pharmacokinetic parameter Cmax.

3. The average mean for T1/2,Tmax and Kel values were 2% lower, 13% lower and 8% higher, respectively, for the test product than for the reference product (Table #6).

Table 8
Mean Plasma Concentrations of Metabolite V in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions (Unit: ng/mL) (Test lot #93250-0100, Ref. Lot #0781255)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	132.36	77.94	171.62	130.14	0.77
0.67	417.13	130.34	456.85	165.09	0.91
1	545.38	143.91	572.35	159.44	0.95
1.33	572.66	133.26	608.29	156.30	0.94
1.67	581.71	126.79	600.90	133.65	0.97
2	583.63	132.49	588.45	129.70	0.99
2.33	576.20	141.22	576.00	137.14	1.00
2.67	541.98	129.09	556.44	161.59	0.97
3	513.45	132.20	539.03	167.34	0.95
3.5	476.20	140.43	493.18	150.24	0.97
4	446.35	146.74	456.18	136.23	0.98
5	389.88	137.61	411.95	150.91	0.95
6	363.76	104.22	383.53	115.01	0.95
8	277.71	101.38	288.20	107.56	0.96
10	252.36	105.89	310.07	121.57	0.81
12	213.29	82.45	249.73	108.36	0.85
14	220.78	100.99	265.23	103.72	0.83
16	192.15	88.77	199.97	75.37	0.96
20	91.95	63.46	86.57	58.60	1.06
24	29.23	50.51	19.99	37.67	1.46

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 9
Arithmetic Mean Metabolite V Pharmacokinetic Parameters in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
*AUCI	6314.06	1644.26	6908.35	1446.73	0.91
AUCT	5879.83	1409.62	6287.13	1392.37	0.94
CMAX	651.80	146.53	680.70	151.41	0.96
KE	0.26	0.12	0.24	0.12	1.08
THALF	3.52	2.22	4.24	3.36	0.83
TMAX	1.72	0.63	1.83	1.09	0.94

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* N=33

Table 10
LSMEANS AND 90% CONFIDENCE INTERVALS
For Metabolite V in 40 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	6040.94	6688.04	0.90	84.27	96.81
LAUCT	5698.17	6135.11	0.93	87.85	98.19
LCMAX	635.95	664.80	0.96	92.60	98.82

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
T/R= Test/Ref. ratios (under fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

1. The mean plasma metabolite V levels reached a maximum level of concentration around 1.33-2.0 hours (Table #8 and the attached Figure #3).

2. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #10). The T/R mean ratios of the LSMEAN for log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25 (Table #9).

   There were no significant sequence or period effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCt, AUCi and Cmax. However, there was a significant treatment effect (p less than 0.05) for the log-transformed pharmacokinetic parameters AUCt, AUCi and Cmax.

3. The average mean for T1/2, Tmax and Kel values were 17% lower, 6% lower and 8% higher, respectively, for the test product than for the reference product (Table #9).

Deficiency Comment #2

On page #186, line #1, Volume #C1.2, the firm provided the following statement 'All analytical runs did not meet acceptance criteria for all analytes'. Please provide a clarification of this statement .

The firm's response to Comment #2.

The firm's response to comment #2 is acceptable.

REVIEWER'S COMMENTS

1. In this amendment the firm has provided satisfactory responses to all the deficiencies that were identified in the previous review (reviewed date October 23, 1996). In addition, the firm reanalyzed all plasma samples for the single-dose study, under fasting conditions using validated assay which utilized an internal standard method such as the one used in post-prandial and multiple-dose studies.

2. Under Fasting Conditions: The firm's single-dose bioequivalence study under fasting conditions demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's **Trental® 400 mg Extended Release Tablets are bioequivalent. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% for Pentoxifylline, Metabolite I and Metabolite V (The results of the statistical analysis are presented in this report).**

3. Under Non-Fasting Conditions: The firm's single-dose bioequivalence study #013-21-10896 under non-fasting conditions demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product,

Hoechst-Roussel's Trental® 400 mg Extended Release Tablets are bioequivalent. The ratios of the test LSMEAN to the reference LSMEAN for AUCt, AUCi and Cmax are within the acceptable range of 0.8-1.2 for Pentoxifylline, Metabolite I and Metabolite V (The results of the statistical analysis are presented in the review dated October 23, 1996).

4. Under Multiple-Dosing Study: The firm's multiple-dose bioequivalence study #013-22-10897 demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets are bioequivalent. The 90% confidence intervals for the log-transformed AUCt and Cmax were within the acceptable range of 80-125% (The results of the statistical analysis are presented in the review dated October 23, 1996).

5. The dissolution testing conducted by ESI Lederle, on its the test product, Pentoxifylline 400 mg Extended Release Tablets (Lot #93250-0100) is acceptable (see the review dated October 23, 1996). The dissolution testing should be conducted in 900 mL of deaerated purified water at 37°C using USP 23 apparatus 2 (Paddle) at 75 rpm. Based on the submitted data the following tentative specification are recommended:

1	hour
6	hours
10	hours
20	hours

RECOMMENDATIONS

1. The three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple-dose steady state) conducted by ESI Lederle comparing its test product Pentoxifylline 400 mg Extended Release Tablets (Lot # 93250-0100) to the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets (Lot #0781255) have been found acceptable by the Division of Bioequivalence. The three studies demonstrated that ESI Lederle's Pentoxifylline 400 mg Extended Release Tablets are bioequivalent to the reference listed drug, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets.

2. The dissolution testing data conducted by ESI Lederle, on its the test product, Pentoxifylline 400 mg Extended Release Tablets (Lot #93250-0100) have been found acceptable.

3. The dissolution testing should be conducted in 900 mL of deaerated purified water at 37°C using USP 23 apparatus 2 (Paddle) at 75 rpm. Based on the submitted data the following tentative specification are recommended:

1 hour
6 hours
10 hours
20 hours

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence.

The firm should be informed of the recommendations.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 6/25/97

Concur: Date: 6/30/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 74-877 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/050797/060397/062097/file #74877a.d96

Attachment
(Tables form the original report dated 10/23/1996))

I. Data Analysis (Under Non-Fasting Conditions):

Table 10
Mean Plasma Concentrations of Pentoxifylline 18 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Non-Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	11.38	17.91	9.71	10.43	36.31	38.68
0.67	25.91	29.19	23.17	15.86	58.13	42.58
1	35.79	24.85	32.87	19.41	51.44	28.43
1.5	52.31	27.49	47.82	33.69	49.37	34.57
2	54.97	31.30	53.41	35.03	49.56	29.90
2.5	61.67	33.12	56.20	35.86	42.67	28.32
3	64.57	36.42	59.58	33.78	41.54	27.56
3.5	63.34	37.45	57.69	30.42	40.86	26.88
4	68.74	47.87	58.42	26.81	32.63	23.21
4.5	75.46	56.94	67.41	37.83	28.41	18.55
5	74.72	49.88	75.49	50.29	26.28	15.34
6	**84.85**	61.92	**85.18**	69.40	35.34	20.96
8	42.79	32.13	47.44	43.25	35.64	26.18
10	56.36	63.70	26.80	15.32	27.93	16.16
12	33.39	34.17	26.68	26.03	23.13	17.89
14	14.10	12.02	14.10	9.78	20.02	17.99
16	8.87	9.42	6.45	6.58	12.55	11.06
20	0.71	2.06	0.73	2.19	6.07	8.58
24	0.00	0.00	0.00	0.00	3.43	5.16

(CONTINUED)

TIME HR	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
0.33	1.17	0.31	0.27
0.67	1.12	0.45	0.40
1	1.09	0.70	0.64
1.5	1.09	1.06	0.97
2	1.03	1.11	1.08
2.5	1.10	1.45	1.32
3	1.08	1.55	1.43
3.5	1.10	1.55	1.41
4	1.18	2.11	1.79
4.5	1.12	2.66	2.37

5	0.99	2.84	2.87
6	1.00	2.40	2.41
8	0.90	1.20	1.33
10	2.10	2.02	0.96
12	1.25	1.44	1.15
14	1.00	0.70	0.70
16	1.37	0.71	0.51
20	0.97	0.12	0.12
24	.	0.00	0.00

MEAN1=Test-Fed MEAN2=Reference-Fed MEAN3=Test-Fast
RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 11
LSMEANS Pharmacokinetic Parameters Pentoxifylline in 18 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Non-Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	918.94	797.76	713.48	1.15	1.29	1.12
AUCT	761.98	668.65	565.49	1.14	1.35	1.18
CMAX	136.62	125.75	80.23	1.09	1.70	1.57
*LAUCI	842.16	754.66	657.39	1.12	1.28	1.15
*LAUCT	649.80	598.57	438.98	1.09	1.48	1.36
*LCMAX	119.54	111.01	64.83	1.08	1.84	1.71

LSM1=LSMEAN Test-Fed LSM2=LSMEAN Ref.-Fed LSM3=LSMEAN Test-Fast
RLSM12=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the LSMEAN (antilog of the means of the logs).

Table 12
Mean Plasma Concentrations of Metabolite I 18 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Non-Fasting Conditions
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	11.28	26.84	9.31	12.95	42.68	47.07
0.67	44.20	48.64	48.83	46.35	146.17	117.96
1	81.06	73.66	78.85	55.38	201.74	143.12
1.5	136.81	83.43	127.14	76.30	231.10	132.61

2	177.29	102.04	166.38	100.35	243.60	131.18
2.5	206.18	108.16	194.76	114.20	241.65	126.80
3	230.60	122.11	224.50	129.01	238.24	127.87
3.5	276.44	144.05	233.82	120.63	235.24	126.65
4	295.36	161.46	256.71	122.09	215.47	112.99
4.5	326.22	204.90	280.31	135.06	194.43	111.71
5	344.28	207.19	335.56	180.37	183.35	103.49
6	368.81	229.29	335.09	181.72	160.92	80.23
8	221.53	156.52	240.68	175.68	135.42	76.89
10	195.44	157.46	154.57	112.27	121.98	67.40
12	153.36	148.67	124.52	93.36	97.41	61.10
14	84.33	69.41	73.97	45.69	82.55	63.00
16	52.16	49.89	46.57	29.52	71.08	69.14
20	14.88	18.69	14.44	13.52	39.38	40.32
24	2.34	5.58	1.57	4.61	21.66	25.32

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.33	1.21	0.26	0.22
0.67	0.91	0.30	0.33
1	1.03	0.40	0.39
1.5	1.08	0.59	0.55
2	1.07	0.73	0.68
2.5	1.06	0.85	0.81
3	1.03	0.97	0.94
3.5	1.18	1.18	0.99
4	1.15	1.37	1.19
4.5	1.16	1.68	1.44
5	1.03	1.88	1.83
6	1.10	2.29	2.08
8	0.92	1.64	1.78
10	1.26	1.60	1.27
12	1.23	1.57	1.28
14	1.14	1.02	0.90
16	1.12	0.73	0.66
20	1.03	0.38	0.37
24	1.50	0.11	0.07

MEAN1=Test-Fed MEAN2=Reference-Fed MEAN3=Test-Fast
RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 13
LSMEAN Pharmacokinetic Parameters Metabolite I
in 18 Subjects Following a Single-Dose
of Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	3355.16	3130.68	2944.85	1.07	1.14	1.06
AUCT	3299.15	2993.81	2704.18	1.10	1.22	1.11
CMAX	484.59	422.10	274.15	1.15	1.77	1.54
*LAUCI	2947.02	2844.10	2591.77	1.04	1.14	1.10
*LAUCT	2894.92	2678.13	2294.34	1.08	1.26	1.17
*LCMAX	429.55	379.89	230.46	1.13	1.86	1.65

LSM1=LSMEAN Test-Fed LSM2=LSMEAN Ref.-Fed LSM3=LSMEAN Test-Fast
RLSM12=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the LSMEAN (antilog of the means of the logs).

Table 14
Mean Plasma Concentrations of Metabolite V
18 Subjects Following a Single-Dose of
Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	30.96	54.83	20.85	25.89	162.13	136.93
0.67	118.56	89.09	113.92	67.41	419.11	182.66
1	193.04	118.61	205.88	107.17	523.50	172.75
1.5	316.61	157.14	305.00	165.76	554.61	124.73
2	359.61	159.62	368.33	180.23	537.33	150.01
2.5	422.72	203.87	421.83	224.45	509.39	148.74
3	484.44	297.96	477.78	249.88	480.94	109.58
3.5	559.94	333.62	488.72	233.34	476.78	127.98
4	593.00	304.80	555.67	227.14	428.39	119.62
4.5	640.06	323.05	618.89	269.89	390.17	103.28
5	639.89	266.26	702.39	256.23	365.22	99.59
6	588.89	175.44	616.22	166.45	331.50	108.45
8	319.72	118.71	407.61	216.56	277.28	89.57
10	372.17	287.03	283.83	125.04	249.06	91.71
12	275.27	219.41	254.06	224.80	198.36	70.96
14	146.83	83.66	165.58	136.89	181.40	83.05
16	98.35	65.33	117.10	107.55	185.93	184.01
20	21.95	31.44	31.35	31.37	99.42	81.35
24	3.79	11.25	3.41	9.94	61.38	66.69

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
0.33	1.48	0.19	0.13
0.67	1.04	0.28	0.27
1	0.94	0.37	0.39
1.5	1.04	0.57	0.55
2	0.98	0.67	0.69
2.5	1.00	0.83	0.83
3	1.01	1.01	0.99
3.5	1.15	1.17	1.03
4	1.07	1.38	1.30
4.5	1.03	1.64	1.59
5	0.91	1.75	1.92
6	0.96	1.78	1.86
8	0.78	1.15	1.47
10	1.31	1.49	1.14
12	1.08	1.39	1.28
14	0.89	0.81	0.91
16	0.84	0.53	0.63
20	0.70	0.22	0.32
24	1.11	0.06	0.06

MEAN1=Test-Fed MEAN2=Reference-Fed MEAN3=Test-Fast
RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 15
LSMEAN Pharmacokinetic Parameters Metabolite V in 18 Subjects Following a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet under Non-Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	5860.80	6009.56	6311.77	0.98	0.93	0.95
AUCT	5642.94	5768.47	5673.60	0.98	0.99	1.02
CMAX	880.43	832.13	610.79	1.06	1.44	1.36
*LAUCI	5772.08	5889.88	6056.64	0.98	0.95	0.97
*LAUCT	5546.26	5639.46	5492.65	0.98	1.01	1.03
*LCMAX	837.33	796.25	597.54	1.05	1.40	1.33

LSM1=LSMEAN Test-Fed LSM2=LSMEAN Ref.-Fed LSM3=LSMEAN Test-Fast
RLSM12=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the LSMEAN (antilog of the means of the logs).

J. Data Analysis (Steady-State):

Table 16
Mean Plasma Concentrations of Pentoxifylline at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
96	50.79	32.88	51.53	25.58	0.99
96.25	67.99	33.72	68.70	45.32	0.99
96.5	105.60	56.84	106.70	77.96	0.99
97	89.86	49.39	99.56	49.67	0.90
97.5	78.98	37.43	83.27	36.61	0.95
98	75.80	38.20	84.92	43.89	0.89
98.5	69.82	28.24	76.96	40.04	0.91
99	60.89	30.08	69.24	31.13	0.88
99.5	59.06	36.86	66.29	32.98	0.89
100	51.96	29.31	51.34	24.17	1.01
101	41.48	22.07	44.97	23.69	0.92
102	64.71	34.14	68.34	45.20	0.95
103	55.00	30.81	56.17	31.56	0.98
104	43.04	23.73	39.68	23.75	1.08

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 17
Arithmetic and Geometric Mean For Pentoxifylline Pharmacokinetic Parameters at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	501.85	224.98	531.58	252.34	0.94
CAVG	62.73	28.12	66.45	31.54	0.94
CMAX	122.14	55.45	129.43	73.52	0.94
CMIN	32.24	19.45	33.80	21.15	0.95
FLUC	1.52	0.62	1.44	0.48	1.05
*LAUCT	450.46	0.50	473.83	0.52	0.95
*LCAVG	56.31	0.50	59.23	0.52	0.95
*LCMAX	109.53	0.50	111.83	0.57	0.98
*LCMIN	27.04	0.62	28.30	0.62	0.96
*LFLUC	1.42	0.36	1.38	0.29	1.03
TMAX	1.29	0.33	1.58	0.33	0.82

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

Table 18
LSMEANS AND 90% CONFIDENCE INTERVALS
For Pentoxifylline at Steady-State (Day-5) in 24 Subjects
After 400 mg of Pentoxifylline ER Tablet
every 8 hours for 13 doses
Unit: ng/mL

	LSMEAN1	LSMEAN2	T/R	LOWCI12	UPPCI12
AUCT	501.85	531.57	0.94	83.69	105.13
CAVG	62.73	66.45	0.94	83.69	105.13
CMAX	122.14	129.42	0.94	82.32	106.42
CMIN	32.24	33.80	0.95	77.77	113.03
FLUC	1.52	1.44	1.06	91.51	119.21
*LAUCT	450.46	473.83	0.95	85.09	106.22
*LCAVG	56.31	59.23	0.95	85.09	106.22
*LCMAX	109.53	111.83	0.98	87.45	109.70
*LCMIN	27.04	28.30	0.96	80.79	113.01
*LFLUC	1.42	1.38	1.03	91.35	115.86

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.
RLSM12=T/R ratios (under non-fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the LSMEAN (antilog of the means of the logs).
AUCT= $AUCT_{96-104}$
CAVG= AUCT/8
CMIN= minimum conc. from time range 96-104 hours
FLUC= [CMAX -CMIN]/CMIN

Table 19
Mean Plasma Concentrations of Metabolite I at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
96	335.19	182.65	325.00	181.20	1.03
96.25	288.80	144.58	284.08	144.81	1.02
96.5	363.85	167.65	361.12	197.18	1.01
97	441.67	204.42	441.21	207.56	1.00
97.5	447.17	205.70	467.92	217.72	0.96
98	439.40	193.95	462.71	207.00	0.95
98.5	426.79	189.48	445.63	187.81	0.96
99	402.75	187.14	426.21	188.22	0.94
99.5	369.08	190.28	394.00	177.45	0.94
100	337.11	186.31	361.42	156.86	0.93
101	295.60	172.03	304.25	142.29	0.97
102	272.17	149.67	274.43	161.29	0.99
103	231.55	134.23	230.13	133.03	1.01
104	207.00	120.63	199.83	119.73	1.04

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 20
Arithmetic and Geometric Mean for Metabolite I Pharmacokinetic Parameters at Steady-State (Day-5) in 24 Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours for 13 doses
Unit: ng/mL

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	2669.65	1304.23	2745.70	1260.37	0.97
CAVG	333.71	163.03	343.21	157.55	0.97
CMAX	470.83	206.35	497.71	215.29	0.95
CMIN	183.95	96.05	190.83	116.20	0.96
FLUC	0.90	0.18	0.93	0.23	0.96
*LAUCT	2375.89	0.51	2479.77	0.48	0.96
*LCAVG	296.99	0.51	309.97	0.48	0.96
*LCMAX	425.34	0.48	452.45	0.47	0.94
*LCMIN	158.10	0.60	160.85	0.62	0.98
*LFLUC	0.89	0.20	0.91	0.26	0.98
TMAX	1.91	0.74	1.80	0.78	1.06

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

Table 21
LSMEANS AND 90% CONFIDENCE INTERVALS
For Metabolite I at Steady-State (Day 5) in
24 Subjects After 400 mg of Pentoxifylline ER Tablet
every 8 hours for 13 doses
Unit: ng/mL

	LSMEAN1	LSMEAN2	T/R	LOWCI12	UPPCI12
AUCT	2669.65	2745.70	0.97	89.64	104.82
CAVG	333.71	343.21	0.97	89.64	104.82
CMAX	470.83	497.71	0.95	87.31	101.90
CMIN	183.95	190.83	0.96	82.53	110.26
FLUC	0.90	0.93	0.97	86.33	106.58
*LAUCT	2375.89	2479.77	0.96	86.53	106.09
*LCAVG	296.99	309.97	0.96	86.53	106.09
*LCMAX	425.34	452.45	0.94	85.94	102.83
*LCMIN	158.10	160.85	0.98	84.58	114.22
*LFLUC	0.89	0.91	0.98	87.87	108.43

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.
RLSM12=T/R ratios (under non-fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the LSMEAN (antilog of the means of the logs).
AUCT= $AUCT_{96-104}$
CAVG= AUCT/8
CMIN= minimum conc. from time range 96-104 hours
FLUC= [CMAX -CMIN]/CMIN

Table 22
Mean Plasma Concentrations of Metabolite V
at Steady-State (Day-5) in 24 Subjects
After 400 mg of Pentoxifylline ER Tablet
every 8 hours for 13 doses
Unit: ng/mL

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
96	770.08	323.94	778.63	329.67	0.99
96.25	648.79	157.08	661.21	208.21	0.98
96.5	841.33	145.83	850.38	240.54	0.99
97	1011.13	197.93	1065.88	286.04	0.95
97.5	976.42	221.05	1042.83	282.48	0.94
98	940.50	239.50	986.13	251.15	0.95
98.5	892.92	220.51	956.42	260.85	0.93
99	843.21	198.64	896.04	234.43	0.94
99.5	765.50	183.95	824.21	210.04	0.93
100	708.71	187.08	747.63	192.31	0.95
101	608.92	173.41	655.29	171.55	0.93
102	598.38	183.22	613.88	185.90	0.97
103	526.21	180.40	534.75	140.96	0.98
104	460.04	138.82	443.88	127.90	1.04

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 23
Arithmetic and Geometric Mean for
Metabolite V Pharmacokinetic Parameters
at Steady-State (Day-5) in 24 Subjects
After 400 mg of Pentoxifylline ER Tablet
every 8 hours for 13 doses
Unit: ng/mL

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	5784.00	1311.92	6053.88	1341.25	0.96
CAVG	723.00	163.99	756.73	167.66	0.96
CMAX	1041.83	217.66	1123.42	255.98	0.93
CMIN	426.04	133.95	421.33	114.78	1.01
FLUC	0.87	0.21	0.94	0.24	0.93
*LAUCT	5651.34	0.22	5872.83	0.27	0.96
*LCAVG	706.42	0.22	734.10	0.27	0.96
*LCMAX	1022.46	0.19	1093.15	0.25	0.94
*LCMIN	405.13	0.33	400.33	0.37	1.01
*LFLUC	0.85	0.24	0.92	0.25	0.93
TMAX	1.29	0.46	1.55	0.92	0.83

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

Table 24
LSMEANS AND 90% CONFIDENCE INTERVALS
For Metabolite V at Steady-State (Day-5)
in 24 Subjects After 400 mg of Pentoxifylline ER
Tablet every 8 hours for 13 doses
Unit: ng/mL

PARAMETER	LSMEAN1	LSMEAN2	T/R	LOWCI12	UPPCI12
AUCT	5784.00	6053.88	0.96	88.77	102.92
CAVG	723.00	756.73	0.96	88.77	102.92
CMAX	1041.83	1123.42	0.93	84.72	100.76
CMIN	426.04	421.33	1.01	91.14	111.10
FLUC	0.87	0.94	0.93	82.61	102.97
*LAUCT	5651.34	5872.83	0.96	88.95	104.10
*LCAVG	706.42	734.10	0.96	88.95	104.10
*LCMAX	1022.46	1093.15	0.94	86.33	101.33
*LCMIN	405.13	400.33	1.01	88.84	115.27
*LFLUC	0.85	0.92	0.92	83.89	103.09

LSMEAN= least squares mean
LSMEAN1=LSMEAN-test LSMEAN2=LSMEAN-ref.
RLSM12=T/R ratios (under non-fasting conditions)
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the antilog of the means of the logs.
AUCT= $AUCT_{96-104}$
CAVG= AUCT/8
CMIN= minimum conc. from time range 96-104 hours
FLUC= [CMAX - CMIN]/CMIN

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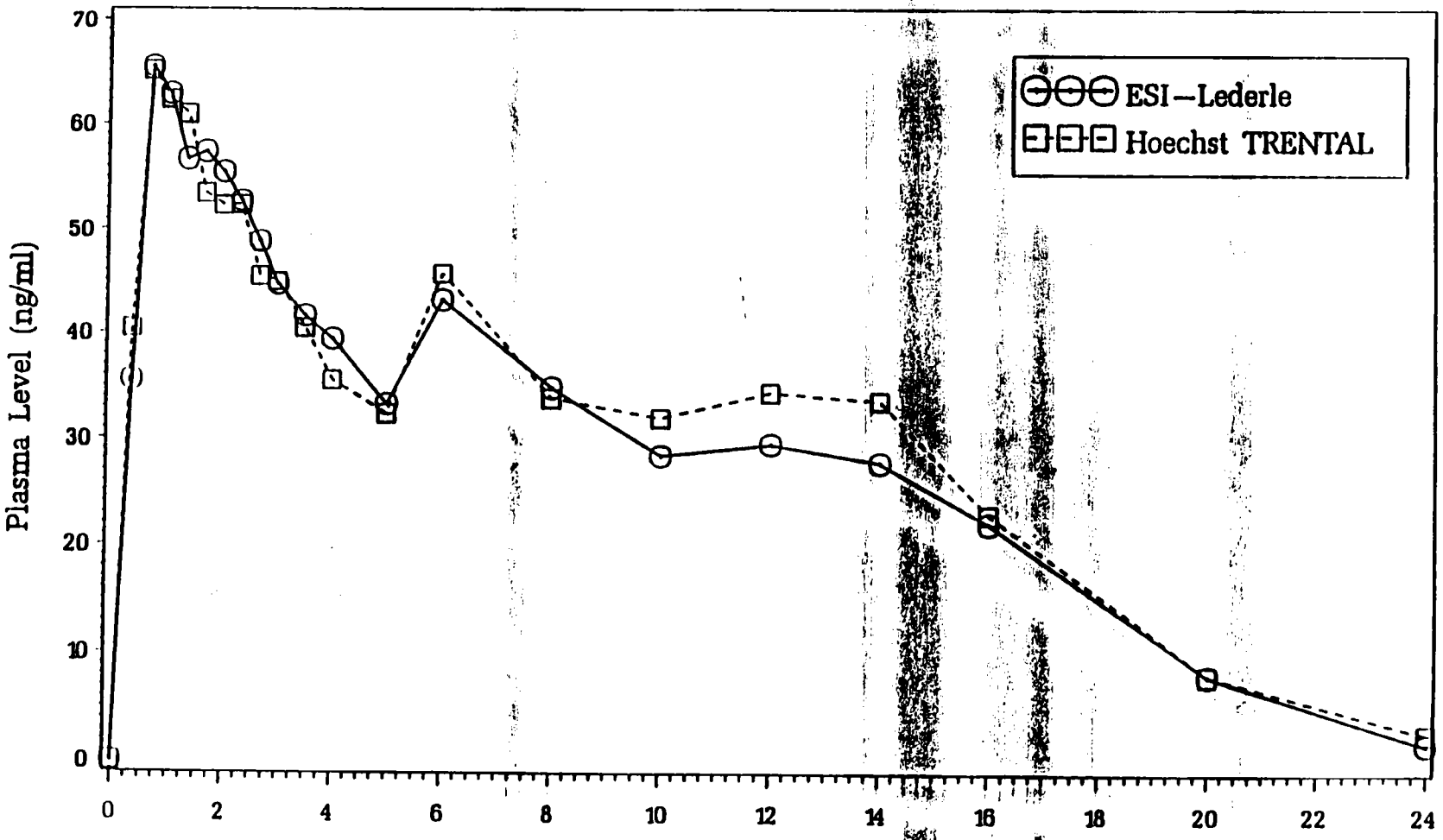
Figure 1: Mean Pentoxifylline Plasma Levels

#013-20-10895, Reassay

N = 40

Under fasting Conditions



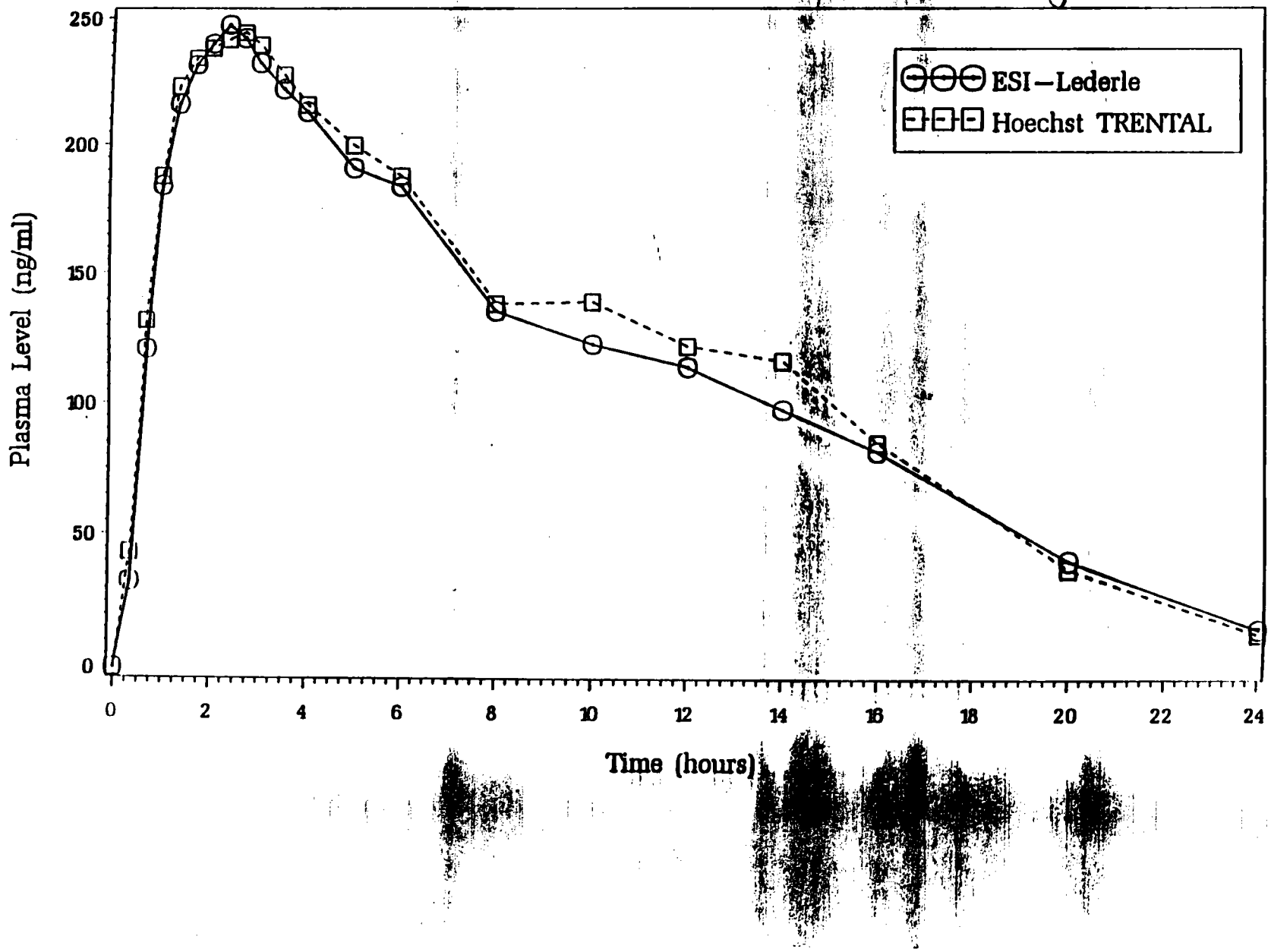
ANDA # 74-877

Figure 2: Mean Metabolite I Plasma Levels

#013—20—10895, Reassay

N = 40

Under fasting Conditions



ANDA #74-877

Figure 3: Mean Metabolite V Plasma Levels

#013–20–10895, Reassay

N = 40

Under fasting Conditions